| Application Type | BLA Original |
| --- | --- |
| STN | 125737/0 |
| CBER Received Date | November 30, 2020 |
| PDUFA Goal Date | November 30, 2021 |
| Division / Office | DVRPA/OVRR |
| Committee Chair | Marian Major |
| Clinical Reviewer | Darcie Everett |
| Project Managers | Sudhakar Agnihothram, Katherine Berkhousen, Paul Keller |
| Priority Review | No |
| Reviewer Name | Jennifer L. Kirk |
| Review Completion Date / Stamped Date | |
| Concurrence | Lei Huang<br>Concurring Reviewer,<br>Viral and Bioassay Team, VEB, DB |
| | Tsai-Lien Lin<br>Branch Chief,<br>Vaccine Evaluation Branch, DB |
| | John Scott<br>Director,<br>Division of Biostatistics, OBE |
| Applicant | VBI Vaccines, Inc. |

| Established Name | Hepatitis B Vaccine (Recombinant) |
|---|---|
| (Proposed) Trade Name | Prehevbrio |
| Pharmacologic Class | Vaccine |
| Formulation, including Adjuvants, etc | 10 µg/mL HBsAg with 0.5 mg/mL aluminum hydroxide |
| Dosage Form and Route of Administration | 1.0mL suspension for intramuscular injection |
| Dosing Regimen | 0, 1, and 6 months |
| Indication and Intended Population | Prevention of infection caused by all known subtypes of hepatitis B virus in adults |

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GLOSSARY

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| AS | Analysis Set |
| BLA | Biologics Licensing Application |
| BMI | Body Mass Index |
| CBER | Center for Biologics Evaluation and Research |
| CI | Confidence Interval |
| DNA | Deoxyribonucleic Acid |
| FAS | Full Analysis Set |
| GMC | Geometric Mean Concentration |
| GMCR | Geometric Mean Concentration Ratio |
| HBsAg | Hepatitis B surface Antigen |
| IND | Investigative New Drug |
| ITT | Intent to Treat Set |
| LLOQ | Lower Limit of Quantitation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PPS | Per Protocol Set |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SPR | Seroprotection Rate |
| TEAE | Treatment Emergent Adverse Event |
| ULOQ | Upper Limit of Quantitation |
| UK | United Kingdom |
| US | United States |

## 1. EXECUTIVE SUMMARY

VBI submitted this original biologics licensing application (BLA 125737/0) to support licensure of Prehevbrio, a recombinant Hepatitis B vaccine, to prevent infection caused by all known subtypes of the hepatitis B virus in adults. Prehevbrio is given at 0, 1, and 6 months and is currently licensed in Israel and Hong Kong.

Two pivotal phase III studies were conducted: Sci-B-Vac-001 and Sci-B-Vac-002. Sci-B-Vac-001 was a multi-center, multinational, randomized, double-blind, parallel-group, active-controlled study in adults ≥ 18 years old who were followed for at least 24 weeks after the third vaccine dose. Sci-B-Vac-001 assessed non-inferiority of the Prehevbrio seroprotection rate compared to that of Engerix-B, a recombinant Hepatitis B vaccine currently licensed in the US, as well as safety. Sci-B-Vac-001 enrolled and randomized 1,607 adults 1:1 to Prehevbrio or Engerix-B, stratified by age group (18–<45, 45–<65, ≥ 65 years) with 80% of participants aged 45 years or older and 40% aged 65 years or older. In Sci-B-Vac-001, the difference in seroprotection rates at 4 weeks after the 3rd dose in adults ≥18 years old, compared to Engerix-B, was 14.88% (95% confidence interval: 11.18%, 18.63%), which met the pre-specified success criterion for non-

inferiority, a lower confidence interval bound for the difference in seroprotection rates > -5%.

Sci-B-Vac-002 was a multi-center, multinational, randomized, double-blind, parallel-group, active-controlled lot consistency and immunogenicity study in adults 18–45 years old who were followed for 24 weeks after the third vaccine dose. Sci-B-Vac-002 enrolled and randomized 2,838 adults 1:1:1:1 to one of 3 lots of Prehevbrio or to Engerix-B, stratified by study site. In Sci-B-Vac-002, the three Prehevbrio lots met the pre-specified success criteria for lot-to-lot consistency and the difference in seroprotection rates at 4 weeks after the 3rd dose, compared to Engerix-B, was 4.49% (95% confidence interval: 2.90%, 6.63%), which also met the pre-specified success criterion.

Across both pivotal studies, 48.4% of Engerix-B and 48.3% of Prehevbrio participants reported unsolicited adverse events within 28 days of any vaccination, and 24 (1.6%) Engerix-B and 74 (2.5%) Prehevbrio participants reported one or more non-fatal severe adverse events through the end of the study. One death was reported in a Sci-B-Vac-002 participant who received Prehevbrio, considered unrelated to study vaccine by the investigator. Similar proportions of participants in the Engerix-B group (12.9%) and in the Prehevbrio group (15.2%) reported adverse events considered vaccine-related. Prehevbrio participants were more likely to report injection site pain (Engerix-B: 44.5%; Prehevbrio: 72.2%), injection site tenderness (Engerix-B: 44.2%; Prehevbrio: 71.2%), and myalgia (Engerix-B: 28.1%; Prehevbrio: 41.7%). Interpretation of the combined safety results may be complicated because although VBI used the same MedDRA version for both studies, the clinical reviewer identified several inconsistencies in the adverse event coding between the two studies. VBI did not assess adverse event coding consistency across the two studies and although the clinical reviewer identified only a few inconsistencies, it is unclear if these comprise all the inconsistencies in the integrated safety dataset.

In general, there were no major statistical issues identified in this submission, and I verified the primary immunogenicity and lot-to-lot consistency results. The non-inferiority of immunogenicity compared to Engerix-B was demonstrated and supports the approval of this vaccine. I defer to the clinical reviewer to assess the regulatory significance of the safety results, given the relatively higher rates of solicited adverse events in Prehevbrio participants and the adverse event coding inconsistencies identified in the integrated safety.

2. CLINICAL AND REGULATORY BACKGROUND

**2.1 Disease or Health-Related Condition Studied**

Please refer to the clinical review.

## 2.2 Currently Available, Pharmacologically Unrelated Treatments and Interventions for the Proposed Indication

There are several recombinant DNA anti-Hepatitis B surface antigen (anti-HBsAg) Hepatitis B vaccines licensed in the US, including Engerix-B. Studies in healthy adolescents and adults (aged 16 through 65 years old) have shown that when given at 0, 1, and 6 months, the seroprotection (antibody titers ≥10 mIU/mL) rate of Engerix-B at 1 month after the 3rd dose is 96%. Among participants aged 40 years and older, when given at 0, 1, and 6 months, the seroprotection rate (SPR) was 88% at 1 month after the 3rd dose.

## 2.4 Previous Human Experience with the Product (Including Foreign Experience)

Prehevbrio is currently licensed in Israel and Hong Kong. Prehevbrio has previously been licensed (sometimes under the name Bio-Hep-B) in several countries in Asia, South America, and Africa.

## 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Several meetings were held with VBI during the pre-IND and IND phases. In an April 10, 2017 pre-IND meeting (CMRTS 10652), CBER recommended that VBI use an alternative method for the confidence intervals for the difference in seroprotection, such as Miettinen and Nurminen's method. CBER also stated that the superiority and exploratory endpoints from Sci-B-Vac-001 would not be labeled.

In the October 3, 2019 meeting (IND 17542/0.28), CBER stated that an integrated safety database including approximately 2,923 participants who received at least one dose of Prehevbrio would be adequate.

In the May 13, 2020 (IND 17542/0.49) pre-BLA meeting, CBER recommended that VBI analyze safety and immunogenicity in the Asian subgroup of Sci-B-Vac-002, despite a small number of participants.

3. Submission Quality and Good Clinical Practices

### 3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

### 3.2 Compliance with Good Clinical Practices and Data Integrity

Please refer to the clinical and bioresearch monitoring reviews.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW
DISCIPLINES

## 4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC and CMC statistical reviews.

## 4.2 Assay Validation

VBI used the VITROS anti-HBsAg assay to assess the immunogenicity of Prehevbrio in
their Phase 3 clinical trials. The validation of the VITROS assay was reviewed under
IND 17542/0.9 and found acceptable.

## 4.3 Clinical

Please refer to the clinical review.

## 4.4 Pharmacovigilance

Please refer to the pharmacovigilance review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE
REVIEW

## 5.1 Review Strategy

This review focuses on the two pivotal phase 3 studies: Sci-B-Vac-001 and Sci-B-Vac-
002. The eleven supportive studies tested a variety of formulations in varying study
designs, and therefore, were only summarized, and not reviewed, in this memo.

Throughout the BLA submission and the remainder of this document, Prehevbrio is
referred to as Sci-B-Vac.

## 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review refers to the documents and datasets from the BLA (BLA 125737/0) in
Module 5.

## 5.3 Table of Studies/Clinical Trials

**Table 1.** Table of Pivotal Clinical Studies

| Study Design Features | Sci-B-Vac-001 | Sci-B-Vac-002 |
|---|---|---|
| Overview | Phase 3 immunogenicity non-inferiority | Phase 3 immunogenicity non-inferiority, lot consistency |
| Countries/Sites | 28 sites: *US: 10* *Finland: 10* *Canada: 7* *Belgium: 1* | 37 sites: *US: 15* *Finland: 10* *Canada: 5* *Belgium: 1* *UK: 4* *Germany: 2* |
| Study Population | adults with stable health ≥18 years old | healthy adults 18-45 years old |
| Treatments | Sci-B-Vac, Engerix-B | Sci-B-Vac, Engerix-B |
| Randomization | 1:1 to treatments, stratified by age group (18–<45, 45–<65, ≥ 65 years) with 80% of participants ≥ 45 and 40% ≥ 65 years old | 1:1:1:1 to Sci-B-Vac lots A, B, C and Engerix-B |
| Primary Objectives | Sci-B-Vac SPR is non-inferior to Engerix-B SPR at 1 month after 3rd dose in adults ≥ 18 years old<br><br>Sci-B-Vac SPR is non-inferior to Engerix-B SPR at 1 month after 3rd dose in adults ≥ 45 years old | Manufacturing equivalence, in terms of immunogenicity, of 3 independent, consecutive lots of Sci-B-Vac at 4 weeks after the 3rd vaccination |
| Secondary Objectives | Sci-B-Vac SPR after 4 and 20 weeks after the 2nd dose is non-inferior to the Engerix-B SPR at 4 weeks after receiving the 3rd dose<br><br>Compare the safety and reactogenicity of Sci-B-Vac and Engerix-B | Sci-B-Vac SPR is non-inferior to Engerix-B SPR at 1 month after 3rd dose in adults ≥ 18 years old<br><br>Compare the safety and reactogenicity of Sci-B-Vac and Engerix-B |
| Sample Sizes (Intent to Treat Populations) | Engerix-B: 811<br><br>Sci-B-Vac: 796 | Engerix-B: 712<br><br>Sci-B-Vac: 2126<br>*Lot A: 711*<br>*Lot B: 709*<br>*Lot C: 706* |

*Source: Created from BLA 125737/0 Integrated Summary of Safety, Table 2 (pp. 12–13) and the Sci-B-Vac-001 and Sci-B-Vac-002 clinical study reports.*

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

**6.1 Sci-B-Vac-001**

This study protocol was titled, "A Phase 3 Double-Blind Randomized Controlled Trial to Compare the Immunogenicity and Safety of a Three-dose Regimen of Sci-B-Vac™ to a Three-dose Regimen of Engerix-B® in Adults (PROTECT)."

6.1.1 Objectives

Co-primary objectives:
- To demonstrate that the seroprotection rate (SPR), i.e., the percent of participants who achieve seroprotection, at 4 weeks (Study Day 196) after completion of the three-dose regimen of Sci-B-Vac is non-inferior to the SPR at 4 weeks after completion of the Engerix-B in adults
- To demonstrate that the SPR at 4 weeks after completion of the three-dose regimen of Sci-B-Vac is superior to the SPR 4 weeks after completion of the three-dose regimen of Engerix-B in older adults ≥ 45 years old

Secondary objectives:
- To determine whether the SPR after receiving two vaccinations of Sci-B-Vac, evaluated at 4 weeks (Study Day 56) and 20 weeks (Study Day 168) after receiving the second vaccine dose, is non-inferior to the SPR at 4 weeks (Study Day 196) after receiving the third vaccine dose of Engerix-B
- To compare the safety and reactogenicity of Sci-B-Vac and Engerix-B

6.1.2 Design Overview

Sci-B-Vac-001 was a multi-center, multinational, randomized, double-blind, parallel-group, active-controlled study in adults ≥ 18 years old who were followed for at least 24 weeks after the third vaccine dose. Blood sampling for immunogenicity was performed at Study Days 0, 28, 56, 168, 196, and 336. Participants were followed for safety endpoints throughout the study.

Approximately 1,546 adults were to be randomized 1:1 to Sci-B-Vac or Engerix-B, stratified by study site and age group (18–<45, 45–<65, and ≥ 65 years old), such that 80% of the study population was ≥ 45 years old and 40% was ≥ 65 years old.

6.1.3 Population

Adults were eligible if they had stable health, including those with well-controlled chronic conditions, had not previously received a hepatitis B vaccine or been infected with hepatitis B, and were not immunocompromised or taking immunosuppressants.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Table 2 describes the study vaccines, both of which were provided as 1mL vials and given on Days 0, 28, and 168.

**Table 2.** Sci-B-Vac-001 Study Vaccines

| Study Vaccines | Name | Single Dose Formulation |
|---|---|---|
| Investigational | Sci-B-Vac | 10μg HBsAg<br>0.5mg Aluminum as aluminum hydroxide |
| Control | Engerix-B | 20μg HBsAg<br>0.5mg Aluminum as aluminum hydroxide |

*Source: Created from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Section 9.4.2 (p. 30).*

6.1.6 Sites and Centers

The study was conducted at 28 centers: 1 in Belgium, 7 in Canada, 10 in Finland, and 10 in the U.S.

6.1.7 Surveillance/Monitoring

Please refer to the clinical and BIMO reviews.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was seroprotection, defined as anti-HBsAg levels $\geq 10$ mIU/mL, at 4 weeks after receiving the third dose of the study vaccine (Study Day 196).

The statistical success criteria for the co-primary objectives were:
- Non-inferiority: a 95% confidence interval (CI) lower bound for the percent difference (Sci-B-Vac minus Engerix-B) in seroprotection rates at week 4 in the study groups $> -5\%$
- Superiority: a 95% CI lower bound for the percent difference (Sci-B-Vac minus Engerix-B) in seroprotection rates at week 4 in the study groups $> 5\%$.

The secondary endpoints were:
- Seroprotection, defined similarly to the primary endpoint, at 4 and 20 weeks after receiving the second Sci-B-Vac dose
- Seroprotection, defined similarly to the primary endpoint, at 4 weeks after receiving the third Engerix-B dose
- Occurrence and severity of adverse events (AEs) and serious adverse events (SAEs)

The statistical success criterion for both secondary immunogenicity endpoints was a 95% CI lower bound for the percent difference (Sci-B-Vac minus Engerix-B) in seroprotection rates in the study groups $> -5\%$.

6.1.9 Statistical Considerations & Statistical Analysis Plan

6.1.9.1 Sample Size and Power
The study was designed to have at least 90% power for each of the co-primary objectives, assuming a two-sided significance level of 0.05 and a true SPR of 0.81 for Engerix-B. Under these assumptions, with a total sample size of 680 participants, the study would have had ≥90% power to demonstrate non-inferiority if the true SPR for Sci-B-Vac was 0.88 and ≥90% power to demonstrate superiority if the true SPR for Sci-B-Vac was 0.96.

6.1.9.2 Analysis Populations
- All Enrolled Set (AS): all screened participants who provided informed consent, baseline demographics, and baseline screening assessments.
- Safety Set: all participants in the AS who received a study vaccine dose, analyzed as vaccinated.
- Intent-to-Treat Set (ITT): all participants in the AS who were randomized; analyzed as randomized.
- Full Analysis Set (FAS): all participants in the AS who received at least one study vaccine dose and provided at least one evaluable sample before and after baseline; analyzed as randomized and defined by timepoint.
- Per-Protocol Set (PPS): all participants in the FAS who received all 3 vaccine doses, had an evaluable sample at baseline and the relevant timepoint, were seronegative at baseline, and had no major protocol deviations that would significantly impact immunogenicity measurements; analyzed as randomized.

6.1.9.3 Analysis for Primary Objectives
The differences in unadjusted SPRs at Day 196 with two-sided, 95% Miettinen and Nurminen CI were reported and used to test the non-inferiority and superiority hypotheses. The co-primary non-inferiority analysis was performed on the PPS, and the co-primary superiority analysis was performed on the FAS participants who were seronegative.

**Statistical Reviewer's Comment:** *The protocol for Sci-B-Vac-001 states that adjusted SPRs will be calculated for the primary immunogenicity objectives, but the statistical analysis plan (SAP) and final report describe unadjusted SPRs and the final report only presents unadjusted SPRs. As the final report is consistent with the SAP, I am not concerned about this discrepancy.*

For the non-inferiority co-primary objective, a sensitivity analysis was conducted using the FAS with and without baseline seronegative participants. For the superiority co-primary objective, a sensitivity analysis was conducted using the ITT with and without baseline seronegative participants. For this analysis, participants with missing immunogenicity measurements at Day 196 were included as failures. For both co-primary

endpoints, a sensitivity analysis using the PPS and a logistic model adjusted for age group was conducted as well.

Subgroup analyses for the primary objectives were performed by gender, body mass index, smoking status, age group, diabetes, alcohol consumption, receipt of non-study licensed vaccine, race, and ethnicity.

6.1.9.4 Analysis for Secondary Immunogenicity Objectives

The differences in unadjusted SPRs with two-sided, 95% Miettinen and Nurminen confidence intervals were reported:
- For Sci-B-Vac at 20 weeks after the second dose (Day 168) versus Engerix-B at Day 196;
- For Sci-B-Vac at 4 weeks after the second dose (Day 56) versus Engerix-B at Day 196.

These confidence intervals were used to test the non-inferiority hypotheses.

**Reviewer's Comment:** *The Sci-B-Vac-001 protocol states that adjusted SPRs will be calculated for the secondary immunogenicity objectives, but the SAP and final report describe and present unadjusted SPRs. As the final report is consistent with the SAP, I am not concerned about this discrepancy.*

Sensitivity analyses for both secondary objectives were performed using the FAS, with and without baseline seropositive participants, and using a logistic regression model adjusted for age group.

Subgroup analyses for the secondary immunogenicity objectives were performed by gender, body mass index, smoking status, age group, diabetes, alcohol consumption, receipt of non-study licensed vaccine, race, and ethnicity.

6.1.9.5 Multiplicity Control

The co-primary objectives were tested sequentially: the superiority hypothesis was tested only if the non-inferiority hypothesis was statistically significant.

If the primary endpoints met their success criteria, the two secondary immunogenicity hypotheses were tested sequentially in the order specified.

**Reviewer's Comment:** *The multiplicity control was adequate because sequential testing controls the family-wise type I error rate.*

6.1.9.6 Analysis for Secondary Safety Objective

Analyses for the safety objective were descriptive and used the Safety Set. Participants who missed a dose were excluded from the Safety Set for that time point.

For solicited local, systemic, and other AEs, the frequency and percentage of participants were presented by vaccine group for participants who provided diary cards and have valid data for each type of AE. Percentages were calculated relative to the number of participants exposed at the visit. Frequencies and percentages were presented by treatment group and by dose and severity for each age group at each time point.

Treatment-emergent AEs (TEAEs) are defined as those that start or worsen on or after the first vaccination date. TEAEs were to be included in the summaries of all AEs within 28 days of each vaccine dose and of the SAEs through the end of the study. TEAEs were to be summarized separately for AEs, SAEs, AEs leading to vaccine withdrawal, AEs leading to study withdrawal, medically attended AEs, and new onset chronic illnesses. Solicited AEs that continued beyond Day 7 were to be counted with the unsolicited AEs.

Unsolicited AEs were to be summarized using frequencies and percentages by severity and causality and by vaccine dose for each vaccine group. AEs; SAEs; unexpected AEs; AEs very likely, probably, or possibly related to vaccine; AEs leading to vaccine withdrawal; AEs leading to study withdrawal; medically attended AEs; new onset chronic illnesses; and solicited AEs continuing beyond Day 7 were to be summarized separately.

6.1.9.6 Missing Data

Anti-HBsAg titers below the lower limit of quantitation (LLOQ) were imputed as one-half the LLOQ. Samples with Anti-HBsAg titers above 1,000 mIU/mL were diluted (b) (4) fold and re-tested if possible, resulting in an upper limit of quantitation (ULOQ) of (b) (4) mIU/mL. Anti-HBsAg titers between 5.0 and 12.0 mIU/mL (inclusive) were considered indeterminate and were re-tested in (b) (4) . If a sample was initially indeterminate, seroprotection status was determined using (b) (4) titers. No missing immunogenicity data were imputed; participants with missing data for the primary and secondary objective analyses were excluded from the corresponding analyses.

AEs with a start date equal to the date of first vaccination or with a missing or unknown start date will be considered treatment emergent. If an AE start or end date is partially missing, the AE will be classified as emerging before or during vaccination if possible. Unknown or missing event severity were treated as potentially life-threatening. Multiple AEs with the same preferred term for the same participant were only counted once. Local and systemic adverse event measurements taken by participants which were considered biologically implausible (see Table 3) were removed.

**Table 3.** Implausible Observations for Participant Reported Safety Outcomes

| Measurement | Implausible Observations |
|---|---|
| Temperature | ≤ 33°C or ≥ 42°C |
| Erythema | < 0mm or ≥ 900mm |
| Induration | < 0mm or ≥ 500mm |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Statistical Analysis Plan 4.0, Table 2 (p.25).*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 2,472 participants were screened, of whom 865 (35%) were not deemed eligible. Therefore, 1,607 participants were enrolled and randomized. Table 4 shows the number of participants per analysis population by treatment group and combined, as well as the percentage of participants from the ITT population in the FAS and PPS.

**Table 4.** Sci-B-Vac-001: Number of Participants (Percent of Intent-to-Treat Set) per Analysis Population by Study Group and in Total

| Analysis Population | Engerix-B | Sci-B-Vac | Total |
|---|---|---|---|
| Safety Set | 811 | 796 | 1607 |
| Intent-to-Treat Set | 811 | 796 | 1607 |
| Full Analysis Set | 803 (99) | 782 (98) | 1585 (99) |
| Per-Protocol Set | 729 (90) | 718 (90) | 1447 (90) |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 13 (p. 62).*

**Reviewer's Comment:** *I have verified these results.*

*6.1.10.1.1 Demographics*

Table 5 shows the demographics of the Safety Set by study group and combined. The distributions of demographic characteristics were similar across treatment groups. A slightly lower percentage of adults aged ≥ 65 years old were enrolled than initially planned. The distribution of demographic characteristics was similar in the PPS.

**Table 5.** Sci-B-Vac-001: Safety Set Demographics by Vaccine Group and Overall

| Demographic* | Engerix-B | Sci-B-Vac | Total |
|---|---|---|---|
| Gender, # (%) | - | - | - |
| *Male* | 303 (37.4) | 315 (39.6) | 618 (38.5) |
| *Female* | 508 (62.6) | 481 (60.4) | 989 (61.5) |
| Race, # (%) | - | - | - |
| *White* | 730 (90.0) | 715 (89.8) | 1445 (89.9) |
| *Asian* | 4 (0.5) | 8 (1.0) | 12 (0.7) |
| *Black or African American* | 65 (8.0) | 66 (8.3) | 131 (8.2) |
| *American Indian or Alaska Native* | 4 (0.5) | 5 (0.6) | 9 (0.6) |
| *Native Hawaiian or Pacific Islander* | 0 | 1 (0.1) | 1 (0.1) |
| *Other* | 8 (1.0) | 1 (0.1) | 9 (0.6) |
| Ethnicity, # (%) | - | - | - |
| *Hispanic or Latino* | 75 (9.2) | 79 (9.9) | 154 (9.6) |
| *Non-Hispanic or Latino* | 732 (90.3) | 714 (89.7) | 1446 (90.0) |
| *Not Collected* | 4 (0.5) | 3 (0.4) | 7 (0.4) |
| Age (years) | - | - | - |
| *Mean (SD)* | 56.6 (13.46) | 56.6 (13.20) | 56.6 (13.33) |
| *Median* | 58.0 | 57.0 | 58.0 |
| *Min, Max* | 18, 90 | 18, 86 | 18, 90 |
| Age Group (years), # (%) | - | - | - |
| *18 - 44* | 154 (19.0) | 145 (18.2) | 299 (18.6) |
| *45 - 64* | 361 (44.5) | 355 (44.6) | 716 (44.6) |
| *≥65* | 296 (36.5) | 296 (37.2) | 592 (36.8) |
| Baseline BMI (kg/m$^2$) | - | - | - |
| *Mean (SD)* | 29.12 (6.390) | 29.42 (6.648) | 29.27 (6.519) |
| *Median* | 27.93 | 28.07 | 28.04 |
| *Min, Max* | 11.3, 63.5 | 13.5, 56.3 | 11.3, 63.5 |
| BMI category (kg/m$^2$), # (%) | - | - | - |
| *>30* | 292 (36.0) | 297 (37.3) | 589 (36.7) |
| *≤ 30* | 519 (64.0) | 499 (62.7) | 1018 (63.3) |
| Smoking Status/Tobacco Use, # (%) | - | - | - |
| *Non-user* | 474 (58.4) | 489 (61.4) | 963 (59.9) |
| *Current user* | 113 (13.9) | 104 (13.1) | 217 (13.5) |
| *Former user* | 224 (27.6) | 203 (25.5) | 427 (26.6) |
| Average Daily Alcohol Consumption, # (%) | - | - | - |
| *0-1 drink* | 744 (91.7) | 733 (92.1) | 1477 (91.9) |
| *2-3 drinks* | 63 (7.8) | 59 (7.4) | 122 (7.6) |
| *≥ 4 drinks* | 4 (0.5) | 4 (0.5) | 8 (0.5) |
| Diabetes Status, # (%) | - | - | - |
| *Diabetic* | 65 (8.0) | 60 (7.5) | 125 (7.8) |
| *Non-diabetic* | 746 (92.0) | 736 (92.5) | 1482 (92.2) |
| Country/Region, # (%) | - | - | - |
| *United States* | 342 (42.2) | 338 (42.5) | 680 (42.3) |
| *Canada* | 133 (16.4) | 126 (15.8) | 259 (16.1) |
| *Europe* | 336 (41.4) | 332 (41.7) | 668 (41.6) |

\* #: number; %: percent of Safety Set; kg: kilograms; m: meters; SD: standard deviation.
*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 14 (pp. 66–68).*

**Reviewer's Comment:** *I have verified the demographic results for the Safety Set and PPS.*

*6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population*
Please refer to the clinical review.

*6.1.10.1.3 Participant Disposition*
Table 6 shows the participant disposition. Of participants who did not receive all three vaccinations, approximately half received two vaccinations (Engerix-B: 62%; Sci-B-Vac: 55%). Almost all of the participants who discontinued vaccination for "other" reasons were participants who withdrew early from the trial. In both treatment groups, the majority of these participants either withdrew consent (not caused by an AE) or were lost to follow-up. A slightly larger proportion of Sci-B-Vac participants discontinued treatment early, with larger proportions of participants discontinuing vaccination because of pregnancy or because they withdrew early from the study.

Among the six Sci-B-Vac participants who discontinued treatment early because they withdrew early from the study for "other" reasons, one participant was enrolled in error, one participant received a prohibited medication, one received non-study vaccinations, one moved away from the study area, one withdrew consent, and one participant could not be vaccinated because an unblinded monitor destroyed all vaccines. Among the two Engerix-B participants who discontinued treatment early because they withdrew early from the study for "other" reasons, both withdrew consent.

*6.1.10.1.4 Protocol Deviations*
A total of 402 (49.6%) Engerix-B and 398 (50%) Sci-B-Vac ITT participants had at least one protocol deviation, and a total of 935 Engerix-B and 944 Sci-B-Vac protocol deviations were reported. The frequencies of participants with each type of protocol deviation were similar in both treatment groups. Participants most frequently reported protocol deviations related to procedures or tests not performed according to protocol: (Engerix-B: 52.3%; Sci-B-Vac: 52.1%) and visit schedule (Engerix-B: 27.9%; Sci-B-Vac: 29.6%).

Of the protocol deviations related to procedures or tests, the majority in both treatment groups resulted from a delay or failure to collected vital signs or safety data and the accidental sharing of unblinded participant data with blinded study staff after the last participant's visit but before database lock at Sites 100, 101, 103, 104, 105, 114, and 115. Two unblinded site-specific product reports were sent via email on April 25, 2019 to 13 blinded site staff at these 7 Canadian sites. Of the 13 staff who received the email, only 2 from sites 105 and 144, had viewed the unblinded reports. Access to the electronic database was revoked for these staff on April 30, 2019 and May 1, 2019.

VBI's contract research organization (b) (4) determined that this event did not impact data integrity because all subject data had been entered and verified from source documents by April 19, 2019 and the only changes to the database from when the email was sent to May 3, 2019 were made in response to queries related to data formatting and preparation for database lock. Furthermore, site staff did not have access to the primary endpoint measure data (anti-HBsAg titers) which were sent from the central lab and incorporated into the database after the database lock for the clinical site data.

Fifty-five (6.8%) of Engerix-B and 42 (5.3%) Sci-B-Vac ITT participants had at least one protocol deviation that led to exclusion from the PPS. Participants excluded from the PPS most frequently reported protocol deviations related to an out-of-window visit: Engerix-B: 38 (69%), Sci-B-Vac-001: 25 (60%).

**Table 6.** Sci-B-Vac-001: Number (Percent) of Safety Set Participants by Disposition or Reason for Early Treatment or Study Discontinuation and Treatment Group or Overall

| Disposition | Engerix-B | Sci-B-Vac | Total |
|---|---|---|---|
| All Enrolled Set | 811 | 796 | 1607 |
| Completed All Vaccinations | 785 (96.8) | 758 (95.2) | 1543 (96.0) |
| Discontinued from Vaccination | 26 (3.2) | 38 (4.8) | 64 (4.0) |
| Completed Study | 769 (94.8) | 756 (95.0) | 1525 (94.9) |
| Early Withdrawal | 42 (5.2) | 40 (5.0) | 82 (5.1) |
| **Primary Reason for Vaccine Discontinuation*** | **Engerix-B** | **Sci-B-Vac** | **Total** |
| Non-serious AE | 3 (0.4) | 3 (0.4) | 6 (0.4) |
| Pregnancy | 0 | 3 (0.4) | 3 (0.2) |
| SAE | 2 (0.2) | 2 (0.3) | 4 (0.2) |
| Other | 21 (2.6) | 30 (3.8) | 51 (3.2) |
| **Primary Reason for Early Withdrawal*** | **Engerix-B** | **Sci-B-Vac** | **Total** |
| Lost to Follow-up | 20 (2.5) | 15 (1.9) | 35 (2.2) |
| Withdrew Consent (not caused by an AE) | 9 (1.1) | 11 (1.4) | 20 (1.2) |
| Moved from Study Area | 3 (0.4) | 2 (0.3) | 5 (0.3) |
| Non-serious AE | 3 (0.4) | 0 | 3 (0.2) |
| Pregnancy | 1 (0.1) | 2 (0.3) | 3 (0.2) |
| Investigator Decision | 1 (0.1) | 1 (0.1) | 2 (0.1) |
| Clinically Significant Change in Medical Condition | 1 (0.1) | 0 | 1 (0.1) |
| Major Protocol Violation | 0 | 1 (0.1) | 1 (0.1) |
| Regulatory Agency, Sponsor or PI Request | 0 | 1 (0.1) | 1 (0.1) |
| SAE | 0 | 1 (0.1) | 1 (0.1) |
| Protocol Non-Compliance | 1 (0.1) | 0 | 1 (0.1) |
| Other | 3 (0.4) | 6 (0.8) | 9 (0.6) |

* AE: Adverse Event, PI: Principal Investigator, SAE: Serious Adverse Event
*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 14, pp.63–64.*

**Reviewer's Comment:** *I have verified these results based on the DS, DV, and EX datasets.*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoints

Table 7 shows the seroprotection results at Day 196 for all age groups in the PPS. The estimated difference in SPRs for all age groups in the PPS was 14.88% (95% CI: 11.18%, 18.63%), which met the pre-specified non-inferiority criterion. Sensitivity results using the FAS and using the PPS with an adjusted logistic regression model were consistent with these results.

**Table 7.** Sci-B-Vac-001: Per-Protocol Set Seroprotection Rates (SPR) at 4 Weeks After the Third Vaccine Dose by Treatment Group with 95% Confidence Intervals (CI)

| Statistic | Engerix-B | Sci-B-Vac |
|---|---|---|
| Evaluated Participants | 723 | 718 |
| Seroprotected Participants | 553 | 656 |
| Seroprotection Rate (SPR) | 76.49% | 91.36% |
| SPR 95% CI | 73.22%, 79.53% | 89.07%, 93.32% |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 19 (p. 72).*

Table 8 shows the seroprotection results at Day 196 for baseline seronegative participants ≥ 45 years of age in the FAS. The estimated difference in SPRs for participants ≥ 45 years of age in the FAS was 16.39% (95% CI: 12.17%, 20.65%), which met the pre-specified superiority criterion. Sensitivity results using the ITT with and without baseline seropositive participants and using the PPS with an adjusted logistic regression model were consistent with these results.

**Table 8.** Sci-B-Vac-001: Full Analysis Set Seroprotection Rates at 4 Weeks After the Third Vaccine Dose by Treatment Group for Participants ≥ 45 Years Old with 95% Confidence Intervals (CI)

| Statistic | Engerix-B | Sci-B-Vac |
|---|---|---|
| Evaluated Participants | 627 | 625 |
| Seroprotected Participants | 458 | 559 |
| Seroprotection Rate (SPR) | 73.05% | 89.44% |
| SPR 95% CI | 69.39%, 76.48% | 86.76%, 91.74% |
| Difference* in SPRs (95% CI) | - | 16.39% (12.17%, 20.65%) |

* Sci-B-Vac minus Engerix-B on the percent scale
*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 21 (p. 77).*

**Reviewer's Comment:** *I have verified the primary endpoint analyses, including the sensitivity analyses.*

6.1.11.2 Analyses of Secondary Endpoints

Table 9 shows the SPRs for Sci-B-Vac at Day 168 (20 weeks after the 2nd vaccination and just before the 3rd vaccination) and for Engerix-B at Day 196 (4 weeks after the 3rd vaccination). The estimated difference in these SPRs was -10.52%
(95% CI: -15.15%, -5.86%), which did not meet the pre-specified non-inferiority criterion. Results using the FAS, including and excluding participants who were baseline seropositive, and using the PPS with a logistic regression model were consistent with these results. Subgroup analyses were also consistent with these results.

**Table 9.** Sci-B-Vac-001: Sci-B-Vac Seroprotection Rates (SPR) at 20 Weeks After the 2nd Vaccination and Engerix-B Seroprotection Rates 4 Weeks After the 3rd Vaccination with 95% Confidence Intervals (CI)

| Statistic | Engerix-B | Sci-B-Vac |
|---|---|---|
| Evaluated Participants | 723 | 717 |
| Seroprotected Participants | 553 | 473 |
| Seroprotection Rate (SPR) | 76.49% | 65.97% |
| SPR 95% CI | 73.22%, 79.53% | 62.37%, 69.44% |
| Difference* in SPRs (95% CI) | - | -10.52% (-15.15%, -5.86%) |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 23 (p. 80).*

Because the first secondary endpoint, non-inferiority of the SPR for Sci-B-Vac at Day 168 to the SPR for Engerix-B at Day 196, did not meet the pre-specified success criterion, the second secondary endpoint, non-inferiority of the SPR for Sci-B-Vac at Day 56 to the SPR for Engerix-B at Day 196, was not tested and no results were presented for this analysis.

**Reviewer's Comment:** *I have verified the secondary endpoint analyses, including the sensitivity analyses.*

6.1.11.3 Subpopulation Analyses

Table 10 shows the seroprotection rates at Day 196 with 95% CIs for each treatment group, along with the differences in seroprotection rates between treatment groups and 95% CIs, in the PPS for important subpopulations. Seroprotection rates were lower for both vaccine groups among participants who were older, male, non-White, Hispanic, diabetic, had a body mass index (BMI) ≥ 30, had on average 1 or more drinks per day, or were a current smoker. Participants from the U.S. tended to have lower seroprotection rates relative to European and Canadian participants, although some confounding factors may apply because U.S. participants were more likely to be older, non-White, Hispanic, diabetic, have a higher BMI, and be a current smoker. These differences were smaller for Sci-B-Vac than for Engerix-B, except for the ≥4 drinks per day subgroup. All subgroups, except for Black/African American race, Other race, and ≥4 drinks per day, had results consistent with the overall results.

Table 11 shows the seroprotection rates at Day 196 with 95% CIs for each treatment group, along with the differences in seroprotection rates between treatment groups and 95% CIs, for baseline seronegative participants ≥ 45 years in the FAS. Trends in the seroprotection rates and differences in seroprotection rates in these subgroups were similar to those observed in the PPS subgroups. All subgroups except 45–49 years old, Black/African American race, Other race, ≥4 drinks per day, and Past Smoker had results consistent with the overall results.

**Reviewer's Comment:** *The subpopulation results should be interpreted with caution as some subgroups were too small to yield precise estimates or adequate power for hypothesis testing, and the hypothesis tests performed by the applicant were neither pre-specified nor adjusted for multiplicity. Overall, the immunogenicity subgroup analyses suggest that the differences in seroprotection rates were consistent across subgroups.*

**Table 10.** Sci-B-Vac-001: Per-Protocol Set Subgroup Seroprotection Rates (SPR) and Seroprotection Rate Differences with 95% Confidence Intervals (CI) by Treatment Group

| Subgroup* | Engerix-B Freq. | Engerix-B SPR (95 CI) | Sci-B-Vac Freq. | Sci-B-Vac SPR (95 CI) | SPR Difference (95% CI) |
|---|---|---|---|---|---|
| **Age Group** | - | - | - | - | - |
| *18-44* | 123/135 | 91.1 (85.0, 95.3) | 124/125 | 99.2 (95.6, 100) | 8.1 (3.4, 14.2) |
| *45-64* | 258/322 | 80.1 (75.3, 84.3) | 308/325 | 94.8 (91.8, 96.9) | 14.6 (9.8, 19.8) |
| *≥65* | 172/266 | 64.7 (58.6, 70.4) | 224/268 | 83.6 (78.6, 87.8) | 18.9 (11.6, 26.1) |
| **Age Category** | - | - | - | - | - |
| *18-39* | 67/72 | 93.1 (84.5, 97.7) | 71/71 | 100 (94.9, 100) | 6.9 (1.6, 15.3) |
| *40-49* | 128/143 | 89.5 (83.3, 94.0) | 156/158 | 98.7 (95.5, 99.8) | 9.2 (4.4, 15.5) |
| *50-59* | 128/164 | 78.0 (70.9, 84.1) | 142/153 | 92.8 (87.5, 96.4) | 14.8 (7.2, 22.5) |
| *60-69* | 165/229 | 72.1 (65.8, 77.8) | 197/221 | 89.1 (84.3, 92.9) | 17.1 (9.9, 24.3) |
| *≥70* | 65/115 | 56.5 (47.0, 65.7) | 90/115 | 78.3 (69.6, 85.4) | 21.7 (9.7, 33.2) |
| **Gender** | - | - | - | - | - |
| *Male* | 187/269 | 69.5 (63.6, 75.0) | 245/282 | 86.9 (82.4, 90.6) | 17.4 (10.6, 24.2) |
| *Female* | 366/454 | 80.6 (76.7, 84.2) | 411/436 | 94.3 (91.7, 96.3) | 13.7 (9.5, 18.0) |
| **Race** | - | - | - | - | - |
| *White* | 506/660 | 76.7 (73.2, 79.8) | 596/648 | 92.0 (89.6, 93.9) | 15.3 (11.5, 19.2) |
| *Black/Af. Am.* | 39/51 | 76.5 (62.5, 87.2) | 49/57 | 86.0 (74.2, 93.7) | 9.5 (-5.4, 54.8) |
| *Other* | 8/12 | 66.7 (34.9, 90.1) | 11/13 | 84.6 (54.6, 98.1) | 18.0 (-16.9, 50.2) |
| **Ethnicity*** | - | - | - | - | - |
| *Hispanic/Lat.* | 45/65 | 69.2 (56.6, 80.1) | 60/67 | 89.6 (79.7, 95.7) | 20.3 (6.8, 33.9) |
| *Non-Hisp./Lat.* | 505/655 | 77.1 (73.7, 80.3) | 593/648 | 91.5 (89.1, 93.5) | 14.4 (10.6, 18.3) |
| **Region** | - | - | - | - | - |
| *United States* | 205/304 | 67.4 (61.9, 72.7) | 255/297 | 85.9 (81.4, 89.6) | 18.4 (11.8, 25.0) |
| *Canada* | 99/120 | 82.5 (74.5, 88.8) | 116/119 | 97.5 (92.8, 99.5) | 15.0 (8.0, 23.1) |
| *Europe* | 249/299 | 83.3 (78.6, 87.3) | 285/302 | 94.4 (91.1, 96.7) | 11.1 (6.2, 16.3) |
| **Diabetes** | - | - | - | - | - |
| *Diabetes* | 35/60 | 58.3 (44.9, 70.9) | 45/54 | 83.3 (70.7, 92.1) | 25.0 (8.4, 40.4) |
| *No Diabetes* | 518/663 | 78.1 (74.8, 81.2) | 611/664 | 92.0 (89.7, 94.0) | 13.9 (10.2, 17.7) |
| **BMI (kg/m$_2$)** | - | - | - | - | - |
| *> 30* | 173/254 | 68.1 (62.0, 73.8) | 240/269 | 89.2 (84.9, 92.7) | 21.1 (14.3, 28.0) |
| *≤ 30* | 380/469 | 81.0 (77.2, 84.5) | 416/449 | 92.7 (89.8, 94.9) | 11.6 (7.4, 16.0) |
| **Alcohol** | | | | | |
| *0-1 Drinks* | 510/662 | 77.0 (73.6, 80.2) | 603/663 | 91.0 (88.5, 93.0) | 13.9 (10.1, 17.8) |
| *2-3 Drinks* | 40/57 | 70.2 (56.6, 81.6) | 51/51 | 100 (93.0, 100) | 29.8 (19.5, 42.7) |
| *≥ 4 Drinks* | 3/4 | 75 (19.4, 99.4) | 2/4 | 50 (6.8, 93.2) | -25.0 (-74.5, 41.5) |
| **Smoking** | - | - | - | - | - |
| *Current Smoker* | 67/95 | 70.5 (60.3, 79.4) | 79/92 | 85.9 (77.0, 92.3) | 15.3 (3.5, 27.0) |
| *Past Smoker* | 153/198 | 77.3 (70.8, 82.9) | 167/187 | 89.3 (84.0, 93.3) | 12.0 (4.7, 19.5) |
| *Non-Smoker* | 333/430 | 77.4 (73.2, 81.3) | 410/439 | 93.4 (90.7, 95.5) | 16.0 (11.4, 20.6) |

| Subgroup* | Engerix-B Freq. | Engerix-B SPR (95 CI) | Sci-B-Vac Freq. | Sci-B-Vac SPR (95 CI) | SPR Difference (95% CI) |
|---|---|---|---|---|---|
| **Non-Study Vac.** | - | - | - | - | - |
| *No Vac.* | 446/587 | 76.0 (72.3, 79.4) | 527/578 | 91.2 (88.6, 93.4) | 15.2 (11.1, 19.4) |
| *Vac.* | 107/136 | 78.7 (70.8, 85.2) | 129/140 | 92.1 (86.4, 96.0) | 13.5 (5.3, 22.0) |

*\* Ethnicity was not collected for 3 Engerix-B and 3 Sci-B-Vac participants in the Per-Protocol Set. These participants are excluded from the Ethnicity results.*
*Source: Created from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report Table 20 (p. 74–75), Figure 3 (p. 76), and Section 14, Table 14.2.1.1.4 .*

**Table 11.** Sci-B-Vac-001: Baseline Seronegative Full Analysis Set Participants ≥ 45 Years Subgroup Seroprotection Rates (SPR) and Seroprotection Rate Differences with 95% Confidence Intervals (CI) by Treatment Group

| Subgroup | Engerix-B: Freq. | Engerix-B: SPR (95% CI) | Sci-B-Vac: Freq. | Sci-B-Vac: SPR (95% CI) | SPR Difference (95% CI) |
|---|---|---|---|---|---|
| Age Group | - | - | - | - | - |
| *45-64* | 275/343 | 80.2 (75.6, 84.3) | 324/342 | 94.7 (91.8, 96.9) | 14.6 (9.8, 19.6) |
| *≥65* | 183/284 | 64.4 (58.6, 70.0) | 235/283 | 83.0 (78.1, 87.2) | 18.6 (11.5, 25.6) |
| Age Category | - | - | - | - | - |
| *45-49* | 74/85 | 87.1 (78.0, 93.4) | 110/112 | 98.2 (93.7, 99.8) | 11.2 (4.44, 20.2) |
| *50-59* | 138/174 | 79.3 (72.5, 85.1) | 149/160 | 93.1 (88.0, 96.5) | 13.81 (6.6, 21.2) |
| *60-69* | 178/247 | 72.1 (66.0, 77.6) | 203/231 | 87.9 (83.0, 91.8) | 15.8 (8.8, 22.8) |
| *≥70* | 68/121 | 56.2 (46.9, 65.2) | 97/122 | 79.5 (71.3, 86.3) | 23.3 (11.7, 34.4) |
| Gender | - | - | - | - | - |
| *Male* | 158/239 | 66.1 (59.7, 72.1) | 211/251 | 84.1 (78.9, 88.4) | 18.0 (10.4, 25.5) |
| *Female* | 300/388 | 77.3 (72.8, 81.4) | 348/374 | 93.0 (90.0, 95.4) | 15.7 (10.9, 20.7) |
| Race | - | - | - | - | - |
| *White* | 416/570 | 73.0 (69.1, 76.6) | 510/565 | 90.3 (87.5, 92.6) | 17.3 (12.9, 21.7) |
| *Black/Af. Am.* | 35/47 | 74.5 (59.7, 86.1) | 40/49 | 81.6 (68.0, 91.2) | 7.2 (-9.6, 24.0) |
| *Other* | 7/10 | 70.0 (34.8, 93.3) | 9/11 | 81.8 (48.2, 97.7) | 11.8 (-26.0, 47.9) |
| Ethnicity* | - | - | - | - | - |
| *Hispanic/Lat.* | 36/57 | 63.2 (49.3, 75.6) | 52/59 | 88.1 (77.1, 95.1) | 25.0 (9.7, 39.8) |
| *Non-Hisp./Lat.* | 418/566 | 73.9 (70.0, 77.4) | 505/564 | 89.5 (86.7, 91.9) | 15.7 (11.3, 20.1) |
| Region | - | - | - | - | - |
| United States | 180/275 | 65.5 (59.5, 71.1) | 227/272 | 83.5 (78.5, 87.7) | 18.0 (10.8, 25.1) |
| Canada | 69/92 | 75.0 (64.9, 83.4) | 88/92 | 95.7 (89.2, 98.8) | 20.7 (11.1, 31.0) |
| Europe | 209/260 | 80.4 (75.0, 85.0) | 244/261 | 93.5 (89.8, 96.2) | 13.1 (7.5, 19.0) |
| Diabetic Status | - | - | - | - | - |
| *Diabetes* | 32/57 | 56.1 (42.4, 69.3) | 45/54 | 83.3 (70.7, 92.1) | 27.2 (10.3, 42.8) |
| *No Diabetes* | 426/570 | 74.7 (71.0, 78.3) | 514/571 | 90.0 (87.3, 92.4) | 15.3 (11.0, 19.7) |
| **BMI (kg/m$_2$)** | - | - | - | - | - |
| >30 | 138/213 | 64.8 (58.0, 71.2) | 187/217 | 86.2 (80.9, 90.5) | 21.4 (13.4, 29.2) |
| ≤30 | 320/414 | 77.3 (73.0, 81.2) | 372/408 | 91.2 (88.0, 93.7) | 13.9 (9.0, 18.8) |
| **Alcohol** | - | - | - | - | - |
| 0-1 Drinks | 422/573 | 73.6 (69.8, 77.2) | 511/574 | 89.0 (86.2, 91.5) | 15.4 (11.0, 19.8) |
| 2-3 Drinks | 34/51 | 66.7 (52.1, 79.2) | 46/48 | 95.8 (85.7, 99.5) | 29.2 (15.0, 43.7) |
| ≥4 Drinks | 2/3 | 66.7 (9.4, 99.2) | 2/3 | 66.7 (9.4, 99.2) | 0.0 (-65.3, 65.3) |
| **Smoking** | - | - | - | - | - |
| Current Smoker | 52/82 | 63.4 (52.0, 73.8) | 72/85 | 84.7 (75.3, 91.6) | 21.3 (8.1, 34.1) |
| Past Smoker | 134/180 | 74.4 (67.4, 80.6) | 149/171 | 87.1 (81.2, 91.8) | 12.7 (4.5, 20.9) |
| Non-smoker | 272/365 | 74.5 (69.7, 78.9) | 338/369 | 91.6 (88.3, 94.2) | 17.1 (11.8, 22.4) |

| Subgroup | Engerix-B: Freq. | Engerix-B: SPR (95% CI) | Sci-B-Vac: Freq. | Sci-B-Vac: SPR (95% CI) | SPR Difference (95% CI) |
|---|---|---|---|---|---|
| **Non-Study Vac.** | - | - | - | - | - |
| No Vac. | 368/505 | 72.9 (68.8, 76.7) | 444/498 | 89.2 (86.1, 91.7) | 16.3 (11.5, 21.1) |
| Vac. | 90/122 | 73.8 (65.0, 81.3) | 115/127 | 90.6 (84.1, 95.0) | 16.8 (7.5, 26.3) |

*\* Ethnicity was not collected for 4 Engerix-B and 2 Sci-B-Vac baseline seronegative participants in the Full Analysis Set. These participants are excluded from the Ethnicity results.*
*Source: Created from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 22 (pp. 78–79).*

6.1.12 Safety Analyses

6.1.12.1 Methods

Participants were given diary cards to record solicited AEs during the week after each vaccination, as well as unsolicited AEs during the 28 days after vaccination. Solicited AEs included local AEs (redness, pain, tenderness, swelling, and itching), systemic AEs (nausea/vomiting, diarrhea, headache, fatigue, myalgia), and what the applicant described as "other AEs" (fever, hypertension, hypotension, tachycardia, bradycardia, and respiratory rate increase or decrease). Solicited local and systemic AEs, as well as fever, were collected up to 7 days after each vaccination. Solicited other AEs, except fever, were collected only for 30 minutes after each vaccination. SAEs, new onset chronic illnesses, and medically attended AEs were collected throughout the study.

6.1.12.3 Deaths

No deaths were reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 62 SAEs were reported in a total of 53 participants. 32 Sci-B-Vac participants (4.0%) reported 35 SAEs, and 21 Engerix-B participants (2.7%) reported 27 SAEs. Atrial fibrillation and colon cancer were reported in 2 participants each in the Engerix-B group, and congestive cardiac failure was reported in 2 Sci-B-Vac participants. All other SAEs were reported in only one participant each. One Sci-B-Vac SAE, viral gastroenteritis, was considered related to Sci-B-Vac by the site investigator. All other SAEs were not considered related to study vaccine. SAEs were more frequent in participants > 45 years old (50 participants, 94.3% of participants with SAEs).

Please refer to the clinical review for a detailed discussion of SAEs.

**Reviewer's Comment:** *I have verified the results described in Sections 6.1.12.3 and 6.1.12.4.*

6.1.12.5 Solicited Adverse Events

Solicited local AEs were reported by 379 (46.7%) Engerix-B and 572 (71.9%) Sci-B-Vac participants. Table 12 shows the frequency of solicited local AEs by vaccine group. Injection site pain and tenderness were the most frequently reported solicited local

adverse events (AEs) in both vaccine groups. Rates of participants reporting specific local solicited AEs were higher for Sci-B-Vac compared to Engerix-B for all solicited local AEs after any dose and after each dose. Rates of participants reporting specific solicited local AEs after each dose were similar to the overall rates and declined with each subsequent dose, although the declines for Sci-B-Vac were modest.

**Table 12.** Sci-B-Vac-001: Number (Percent) of Participants Reporting Specific Solicited Local Adverse Events in the 7 Days After Any Vaccine Dose by Vaccine Group

| Adverse Event | Engerix-B | Sci-B-Vac |
|---|---|---|
| Pain | 294 (36.3) | 503 (63.2) |
| Tenderness | 282 (34.8) | 484 (60.8) |
| Itching | 66 (8.1) | 76 (9.5) |
| Redness | 15 (1.8) | 18 (2.3) |
| Swelling | 12 (1.5) | 18 (2.3) |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 32 (p. 102).*

Rates of participants reporting grade 3 and 4 solicited local AEs were similar between the two vaccines. A total of 12 grade 4 AEs of swelling or erythema were reported, although VBI noted that in all cases, the reaction was graded "potentially life-threatening" because of self-reported skin necrosis at the injection site and that the erythema or swelling would otherwise have been graded "mild." The majority of solicited local AEs onset within 1–3 days after vaccination and lasted a median of 1–2 days for both vaccines. Rates of solicited local adverse events were generally similar for Sci-B-Vac and Engerix-B within each age group and were lower for older age groups.

Solicited systemic AEs were reported by 396 (48.8%) Engerix-B and 445 (55.9%) Sci-B-Vac participants. Table 13 shows the frequency of solicited systemic AEs by vaccine group. The most frequently reported solicited systemic AEs were fatigue, headache, and myalgia. Rates of participants reporting specific solicited systemic AEs were generally comparable, except for myalgia, which Sci-B-Vac participants reported at a higher rate. Rates of participants reporting specific solicited systemic AEs after each dose were similar to those overall and declined with each subsequent dose, although the declines for Sci-B-Vac were modest.

**Table 13.** Sci-B-Vac-001: Number (Percent) of Participants Reporting Specific Solicited Systemic Adverse Events in the 7 Days After Any Vaccine Dose by Vaccine Group

| Adverse Event | Engerix-B | Sci-B-Vac |
|---|---|---|
| Fatigue | 249 (30.7) | 242 (30.4) |
| Headache | 238 (29.3) | 249 (31.3) |
| Myalgia | 197 (24.3) | 276 (34.7) |
| Diarrhea | 96 (11.8) | 82 (10.3) |
| Nausea/Vomiting | 73 (9.0) | 56 (7.0) |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-001 Clinical Study Report, Table 38 (pp. 108–109).*

Rates of participants reporting grade 3 solicited systemic events were similar for the two vaccines (Engerix-B: 2.3%, Sci-B-Vac: 1.6%). The only grade 4 solicited systemic AE was fatigue reported by a Sci-B-Vac participant that was associated with medically-attended bronchitis. Most solicited systemic AEs had an onset of 1 to 4 days after vaccination and had a median duration of 1 to 2 days.

Solicited other AEs were reported by 474 (58.4%) Engerix-B participants and 476 (59.8%) Sci-B-Vac participants. The majority of solicited other AEs reported were grade 1 or 2 and occurred within 30 minutes of vaccination. No grade 4 events were reported. Rates of participants reporting specific solicited other AEs were similar across the two vaccine groups, with a slightly higher rate of bradycardia reported for Sci-B-Vac. Hypertension was the most frequently reported solicited other AE and the most frequently reported grade 3 solicited other AE in both vaccine groups. Rates of participants reporting any solicited other AE were higher in the older age groups for both vaccines, and the rates of grade 3 bradycardia and systolic hypertension appear to increase with age for both vaccines. One participant with pre-existing hypotension met the treatment discontinuation rule for grade 3 hypotension within 24 hours of vaccination.

Solicited AEs that lasted beyond Day 7 were reported by 93 (11.5%) Engerix-B and 81 (10.2%) Sci-B-Vac participants. The most frequent solicited AEs that lasted beyond Day 7 were fatigue, injection site pain, headache, and myalgia. Most solicited AEs that lasted beyond Day 7 were mild or moderate in severity. Eight (1.0%) Engerix-B and five (0.6%) Sci-B-Vac participants reported grade 3 solicited AEs that lasted beyond 7 days. No grade 4 events lasted beyond 7 days. One Sci-B-Vac participant reported injection site bruising through the end of the study.

**Reviewer's Comment:** *I have verified the results described in Section 6.1.12.5, Table 12, and Table 13 of this document, as well as the results in Tables 32–45 of the Sci-B-Vac-001 Clinical Report.*

6.1.12.6 Unsolicited Adverse Events

Within 28 days of any vaccine dose, 389 (48.0%) Engerix-B and 369 (46.4%) Sci-B-Vac participants reported at least one unsolicited AE. Rates of participants reporting at least one unsolicited AE for AEs reported by at least 1% of each vaccine group were similar by system organ class and preferred term. The most common unsolicited AEs in both vaccine groups were infections and infestations, specifically upper respiratory tract infections and nasopharyngitis. Other frequently reported unsolicited AEs included headache, fatigue, myalgia, and back pain. Results were generally similar for rates of participants reporting at least one unsolicited AE through the end of the study.

The majority of participants with unsolicited AEs reported within 28 days of any vaccination reported AEs that were mild or moderate in severity. Grade 3 unsolicited AEs within 28 days of any vaccination were reported by 55 (6.8%) Engerix-B and 46 (5.8%)

Sci-B-Vac participants. Grade 4 unsolicited AEs within 28 days of any vaccination were reported by 7 (0.9%) Engerix-B and 2 (0.3%) Sci-B-Vac participants.

Rates of vaccine-related unsolicited AEs within 28 days after any vaccination were similar, with 99 (12.2%) Engerix-B and 121 (15.3%) Sci-B-Vac participants reporting vaccine-related unsolicited AEs. The most common vaccine-related unsolicited AEs were fatigue, injection site pain, and headache; most were solicited AEs that continued beyond Day 7. Excluding solicited AEs that continued beyond Day 7, the most common vaccine-related unsolicited AEs were dizziness, headache, upper respiratory tract infection, and musculoskeletal stiffness. No grade 4 unsolicited AEs were assessed as vaccine-related. Fatigue and myalgia were the only grade 3 vaccine-related unsolicited AEs reported by more than one Engerix-B participant; these were all solicited AEs that continued beyond Day 7. No vaccine-related unsolicited AEs were reported by more than one Sci-B-Vac participant.

**Reviewer's Comment:** *I have verified the results described in Section 6.1.12.6 and in Tables 46 and 47 (pp. 119–121).*

6.1.12.7 Clinical Test Results

Please refer to the clinical review.

6.1.12.8 Dropouts and/or Discontinuations

A total of 11 participants withdrew from treatment because of AEs: 5 Engerix-B and 6 Sci-B-Vac participants. None of the AEs that led to treatment withdrawal were reported by more than one participant. Three participants discontinued treatment because of vaccine-related AEs: one Engerix-B participant with myalgia and polymyalgia rheumatica, one Sci-B-Vac participant with a swollen tongue and upper respiratory infection, and one Sci-B-Vac participant with gastroenteritis.

A total of four participants discontinued the study because of an AE: one Sci-B-Vac participant with viral gastroenteritis that was serious and assessed as vaccine-related, one Engerix-B participant with myalgia and polymyalgia rheumatica, one Engerix-B participant with herpetic cancer, and one Engerix-B participant with depression. The myalgia and polymyalgia rheumatic were severe and assessed as related to the vaccine.

Treatment discontinuation rules were met for four participants: one Engerix-B participant with grade 4 asthma within 7 days of third vaccine, one Engerix-B participant with grade 4 cholelithiasis within 7 days of first vaccine, one Sci-B-Vac participant with grade 3 hypotension within 24 hours of first vaccination, and one Sci-B-Vac participant with grade 3 viral gastroenteritis within 7 days of vaccination (originally reported as grade 4).

**Reviewer's Comment:** *I could not verify the results for participants who met the treatment discontinuation rules for Engerix-B. I found two Engerix-B participants meeting the treatment discontinuation rules, one with aortic stenosis and atrioventricular*

*block and one with asthma. I also found that the grade 4 cholelithiasis occurred on Day 8 after the first vaccination.*

### 6.2 Sci-B-Vac-002

This study protocol was titled, "A Double-Blind Randomized Controlled Trial to Assess the Lot-to-lot Consistency of Sci-B-Vac™ in Adults (CONSTANT)."

6.2.1 Objectives

Primary Objective:
- To demonstrate manufacturing equivalence, in terms of immunogenicity, of three independent, consecutive lots of Sci-B-Vac at 4 weeks after the third vaccination.

Secondary Objectives:
- To demonstrate that the seroprotection rate (SPR) at 4 weeks after completion of a Sci-B-Vac 3-dose regimen is non-inferior to an Engerix-B 3-dose regimen
- To assess the safety and reactogenicity of Sci-B-Vac compared to Engerix-B

6.2.2 Design Overview

Sci-B-Vac-002 was a multi-center, multinational, randomized, double-blind, parallel-group, active-controlled lot consistency study in adults 18–45 years old who were followed for 24 weeks after the third vaccine dose. Approximately 3,200 adults were randomized 1:1:1:1 to one of three lots of Sci-B-Vac or to Engerix-B, stratified by study site using permuted blocks. Participants were followed for at least 48 weeks, including at least 24 weeks after the 3rd vaccination. Blood samples for immunogenicity assessments were taken at study Days 0 (pre-vaccination), 168 (prior to 3rd vaccination), 196 (4 weeks after 3rd vaccination), and 336 (24 weeks after 3rd vaccination).

In October 2018, VBI closed enrollment early after 2,838 participants were randomized, because the enrollment was extremely slow even after they added additional clinical sites and employed a recruitment company.

6.2.3 Population

Healthy adults were eligible if they had not previously received a hepatitis B vaccine or been infected with hepatitis B, did not have a positive hepatitis C serology test, and were not taking immunosuppressants. Adults with some chronic diseases, such as diabetes, and history of certain cancer in the past 5 years were not eligible.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Sci-B-Vac-002 used the same treatments as Sci-B-Vac-001, described in Table 2 in Section 6.1.4. The three different lots of Sci-B-Vac are designated Lots A, B, and C.

6.2.6 Sites and Centers

Sci-B-Vac-002 had 37 sites: 1 in Belgium, 5 in Canada, 10 in Finland, 2 in Germany, 4 in the United Kingdom, and 15 in the United States.

6.2.7 Surveillance/Monitoring

Please refer to the clinical review.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint was anti-HBsAg levels 4 weeks after the third study vaccine dose.

The secondary endpoints were:
- Seroprotection, defined as anti-HBsAg levels $\geq 10$ mIU/mL, 4 weeks after the third study vaccine dose
- Occurrence and severity of AEs and SAEs.

The statistical success criteria for the primary objective was a 95% confidence interval for the ratio of geometric mean concentrations (GMC) of anti-HBsAg between each pair of Sci-B-Vac lots at 4 weeks after the third vaccination within [0.67, 1.5].

The statistical success criteria for the secondary non-inferiority objective was a 95% CI lower bound for the percent difference (Sci-B-Vac minus Engerix-B) in seroprotection rates at week 4 after the third vaccine dose $> -5\%$.

6.2.9 Statistical Considerations & Statistical Analysis Plan

6.2.9.1 Sample Size and Power

The study was designed to have at least 90% power to ensure that the 95% CI for the difference in $log_{10}$-transformed GMCs between each pair of Sci-B-Vac lots would have a lower bound $> -0.176$ and an upper bound $< 0.176$, assuming the true standard deviation is $\leq 0.9$ on $log_{10}$ scale. Such power was achieved if each treatment group had 800 participants.

If the three Sci-B-Vac lots were combined to test that the Sci-B-Vac SPR is non-inferior to the Engerix-B SPR at 4 weeks after the third vaccine dose, the study was designed to have $> 90\%$ power for a 0.025 non-inferiority test with a margin of -5%, assuming 10% of the participants would be non-evaluable and response rates of at least 85% for Sci-B-Vac and 80% for Engerix-B.

With 700 participants per study group, under the assumptions given above, the study had at least 80% power to demonstrate lot-to-lot consistency and non-inferiority of the SPRs.

6.2.9.2 Analysis Populations

- All Enrolled Set (AS): all screened participants who provided informed consent, baseline demographics, and baseline screening assessments.
- Safety Set: all participants in the AS who received a study vaccine dose, analyzed as vaccinated.
- Intent-to-Treat (ITT): all participants in the AS who were randomized; analyzed as randomized.
- Full Analysis Set (FAS): all participants in the AS who received at least one study vaccine dose and provided at least one evaluable sample at and after baseline; analyzed as randomized and defined by timepoint.
- Per-Protocol Set 1 (PPS1): all participants in the FAS who received all 3 doses of their randomized vaccine, had an evaluable sample at baseline and the relevant timepoint, were seronegative at baseline, and had no major protocol deviations (wrong treatment, prohibited concomitant medication, did not meet entry criteria, etc.); analyzed as treated.
- Per-Protocol Set 2 (PPS2): all participants in PPS1 who attended study visits 3 and 4 within the protocol-specified window; analyzed as treated.

6.2.9.3 Analysis for Primary Objective

The adjusted GMCs at 4 weeks after the third vaccine dose with two-sided, 95% CIs were reported by study group, and GMC ratios (GMCRs) for each pair of Sci-B-Vac lots with 95% CIs were presented, along with the equivalence test results. Adjusted GMCs were calculated using an analysis of covariance (ANCOVA) model adjusted for the logarithmic-scale baseline anti-HBsAg titer.

Originally, the primary analysis was based on PPS1 and PPS2, and if equivalence was demonstrated in either analysis set, manufacturing consistency would be concluded. Based on CBER feedback, the final primary analysis used the PPS1, and the PPS2 analysis was considered a sensitivity analysis. No missing immunogenicity data were imputed; participants with missing data for the primary objective analyses were excluded. A sensitivity analysis, as described above but using the FAS with and without baseline seronegative participants, was conducted.

6.2.9.4 Analysis for Secondary Immunogenicity Objectives

The differences in SPRs with two-sided, 95% Miettinen and Nurminen confidence interval were reported to compare the SPRs at four weeks after the third dose of study vaccine for the pooled Sci-B-Vac lots versus Engerix-B. These confidence intervals were used to test the non-inferiority hypotheses, based on the PPS2 analysis set.

Sensitivity analyses were performed as for the main analysis but using the FAS and ITT, with and without baseline seropositive participants. Subgroup analyses for the secondary

immunogenicity objectives were performed by gender, body mass index, smoking status, age group, diabetes, alcohol consumption, receipt of non-study licensed vaccine, race, and ethnicity.

## 6.2.9.5 Multiplicity Control

The primary and secondary objectives were to be tested sequentially: the secondary hypothesis was only to be tested if the primary hypothesis was statistically significant.

**Statistical Reviewer's Comment:** *For the primary objective, because all 3 pairwise comparisons must meet the pre-specified acceptance criterion to establish lot-to-lot consistency, no multiplicity adjustment was needed. No multiplicity adjustment was needed for the primary and secondary objectives, as the sequential testing procedure controls the family-wise type 1 error rate.*

## 6.2.9.6 Analysis for Secondary Safety Objective

Analyses for the safety objective were descriptive and are the same as those for Sci-B-Vac-001 (see Section 6.1.9.6). Descriptive statistics were presented for each treatment group separately and for the Sci-B-Vac lots combined, using the Safety Set.

## 6.2.9.7 Exploratory and Post-Hoc Analyses

Exploratory analyses included estimating the difference in seroprotection rates between the Sci-B-Vac group at 20 weeks after the second vaccine dose and the Engerix-B group at 4 weeks after the third vaccine dose. This analysis was analogous to the secondary immunogenicity objective analysis (see Section 6.2.9.4).

A post-hoc immunogenicity analysis in the Asian subgroup was performed at CBER's request. Seroprotection rates and mean GMCs were calculated for Days 168, 196, and 336, as well as the proportion of participants who achieved anti-HBsAg titers ≥ 100 mIU/mL by vaccine group, combining Sci-B-Vac lots.

## 6.2.9.8 Imputed and Missing Data

Imputation of immunogenicity data and missing safety data were handled similarly to Sci-B-Vac-001 (see Section 6.1.9.6).

## 6.2.10 Study Population and Disposition

### 6.2.10.1    Populations Enrolled/Analyzed

A total of 4,452 participants were screened, of whom 1,614 (36%) failed screening. Therefore, 2,838 participants were enrolled and randomized. Table 14 shows the number

of participants per analysis population by treatment group and combined, as well as the percent of participants from the ITT population in the FAS, PPS1, and PPS2.

**Table 14.** Sci-B-Vac-002: Number and Percent (of Intent to Treat Set in Parentheses) of Participants per Analysis Population by Study Group and in Total

| Analysis Set | Engerix-B | Sci-B-Vac Lot A | Sci-B-Vac Lot B | Sci-B-Vac Lot C | Sci-B-Vac Total | Total |
|---|---|---|---|---|---|---|
| Safety | 712 | 711 | 708 | 705 | 2124 | 2836 |
| ITT | 712 | 711 | 709 | 706 | 2126 | 2838 |
| FAS | 673 (94.5) | 650 (91.4) | 661 (93.2) | 656 (92.9) | 1967 (92.5) | 2640 (93.0) |
| PPS 1 | 642 (90.2) | 620 (87.2) | 622 (87.7) | 627 (88.8) | 1869 (87.9) | 2511 (88.5) |
| PPS 2 | 603 (84.7) | 590 (83.0) | 591 (83.4) | 597 (84.6) | 1778 (83.6) | 2381 (83.9) |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Table 14 (p. 61).*

### 6.2.10.1.1 Demographics

Table 15 shows the demographics of the Safety Set by study group and combined. The distributions of demographic characteristics were similar across treatment groups. The distribution of demographic characteristics was similar in the ITT, FAS, PPS1, and PPS2.

**Reviewer's Comment:** *I have verified the demographic results for the Safety Set, FAS, ITT, PPS1, and PPS2.*

**Table 15.** Sci-B-Vac-002: Safety Set Demographics by Vaccine Group and Overall

| Demographic* | Engerix-B | Sci-B-Vac Lot A | Sci-B-Vac Lot B | Sci-B-Vac Lot C | Sci-B-Vac Combined | Total |
|---|---|---|---|---|---|---|
| Gender, # (%) | - | - | - | - | - | - |
| *Male* | 291 (40.9) | 303 (42.6) | 313 (44.2) | 291 (41.3) | 907 (42.7) | 1198 (42.2) |
| *Female* | 421 (59.1) | 408 (57.4) | 395 (55.8) | 414 (58.7) | 1217 (57.3) | 1638 (57.8) |
| Race, # (%) | - | - | - | - | - | - |
| *White* | 654 (91.9) | 650 (91.4) | 641 (90.5) | 650 (92.2) | 1941 (91.4) | 2595 (91.5) |
| *Asian* | 9 (1.3) | 9 (1.3) | 15 (2.1) | 13 (1.8) | 37 (1.7) | 46 (1.6) |
| *Black or African American* | 38 (5.3) | 46 (6.5) | 43 (6.1) | 34 (4.8) | 123 (5.8) | 161 (5.7) |
| *American Indian or Alaska Native* | 2 (0.3) | 2 (0.3) | 1 (0.1) | 3 (0.4) | 6 (0.3) | 8 (0.3) |
| *Other* | 9 (1.3) | 4 (0.6) | 8 (1.1) | 5 (0.7) | 17 (0.8) | 26 (0.9) |
| Ethnicity, # (%) | - | - | - | - | - | - |
| *Hispanic or Latino* | 74 (10.4) | 64 (9.0) | 70 (9.9) | 61 (8.7) | 195 (9.2) | 269 (9.5) |
| *Non-Hispanic or Latino* | 636 (89.3) | 643 (90.4) | 638 (90.1) | 643 (91.2) | 1924 (90.6) | 2560 (90.3) |
| *Not Collected* | 2 (0.3) | 4 (0.6) | 0 | 1 (0.1) | 5 (0.2) | 7 (0.2) |
| Age (years) | - | - | - | - | - | - |
| *Mean (SD)* | 33.4 (8.10) | 33.8 (7.96) | 32.9 (8.00) | 33.9 (7.91) | 33.5 (7.97) | 33.5 (8.00) |
| *Median* | 35.0 | 36.0 | 34.0 | 36.0 | 35.0 | 35.0 |
| *Min, Max* | 18, 45 | 18, 45 | 18, 45 | 18, 45 | 18, 45 | 18, 45 |
| BMI (kg/m2) | - | - | - | - | - | - |
| *Mean (SD)* | 25.69 (4.103) | 25.92 (4.215) | 25.75 (3.968) | 25.97 (4.170) | 25.88 (4.118) | 25.83 (4.114) |
| *Median* | 24.97 | 25.68 | 25.37 | 25.73 | 25.55 | 25.43 |
| *Min, Max* | 16.3, 34.9 | 16.1, 34.9 | 16.3, 34.9 | 13.9, 34.9 | 13.9, 34.9 | 13.9, 34.9 |
| BMI Category (kg/m2) , # (%) | - | - | - | - | - | - |
| ≤30 | 595 (83.6) | 576 (81.0) | 591 (83.5) | 570 (80.9) | 1737 (81.8) | 2332 (82.2) |
| >30 | 117 (16.4) | 135 (19.0) | 117 (16.5) | 135 (19.1) | 387 (18.2) | 504 (17.8) |
| Smoking Status/Tobacco use, # (%) | - | - | - | - | - | - |
| *Current user* | 136 (19.1) | 139 (19.5) | 142 (20.1) | 125 (17.7) | 406 (19.1) | 542 (19.1) |

| Demographic* | Engerix-B | Sci-B-Vac Lot A | Sci-B-Vac Lot B | Sci-B-Vac Lot C | Sci-B-Vac Combined | Total |
|---|---|---|---|---|---|---|
| *Former user* | 141 (19.8) | 137 (19.3) | 131 (18.5) | 136 (19.3) | 404 (19.0) | 545 (19.2) |
| *Non-user* | 435 (61.1) | 435 (61.2) | 435 (61.4) | 443 (62.8) | 1313 (61.8) | 1748 (61.6) |
| Average Daily Alcohol Consumption, # (%) | - | - | - | - | - | - |
| *0-1 drink* | 653 (91.7) | 673 (94.7) | 660 (93.2) | 659 (93.5) | 1992 (93.8) | 2645 (93.3) |
| *2-3 drinks* | 54 (7.6) | 32 (4.5) | 45 (6.4) | 43 (6.1) | 120 (5.6) | 174 (6.1) |
| *≥ 4 drinks* | 5 (0.7) | 6 (0.8) | 3 (0.4) | 3 (0.4) | 12 (0.6) | 17 (0.6) |
| Country/Region, # (%) | - | - | - | - | - | - |
| *United States* | 188 (26.4) | 191 (26.9) | 186 (26.3) | 185 (26.2) | 562 (26.5) | 750 (26.4) |
| *Canada* | 31 (4.4) | 31 (4.4) | 29 (4.1) | 30 (4.3) | 90 (4.2) | 121 (4.3) |
| *Europe* | 493 (69.2) | 489 (68.8) | 493 (69.6) | 490 (69.5) | 1472 (69.3) | 1965 (69.3) |

* #: number; %: percent of Safety Set; kg: kilograms; m: meters; SD: standard deviation.
*Source: Adapted from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Table 17 (pp. 67–69).*

*6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population*
Please refer to the clinical review.

*6.2.10.1.3 Participant Disposition*
Table 16 shows the participant disposition. Of participants who did not receive all three vaccinations, most received two vaccinations (Engerix-B: 76%, Sci-B-Vac: 65%). Participants in the Sci-B-Vac groups were slightly more likely to discontinue treatment early compared to the Engerix-B Group, with larger proportions of participants in the Sci-B-Vac groups discontinuing vaccination because of pregnancy, non-serious AEs, or other. Almost all of the participants who discontinued vaccination for "other" reasons were participants who withdrew early from the trial. In all treatment groups, the majority of these participants either were lost to follow-up, withdrew consent (not caused by an adverse event), or moved out of the study area.

*6.2.10.1.4 Protocol Deviations*
A total of 424 (59.6%) Engerix-B and 1,268 (59.6%) Sci-B-Vac ITT participants had at least one protocol deviation, and a total of 1,319 Engerix-B and 4,136 Sci-B-Vac protocol deviations were reported. Participants with at least one protocol deviation in the Sci-B-Vac group were evenly distributed across the three lots. The frequency of participants with each type of protocol deviation was similar in both treatment groups. Participants most frequently reported protocol deviations as related to visit schedules (Engerix-B: 44.2%; Sci-B-Vac: 45.0%) and procedures or tests not performed according to protocol (Engerix-B: 44.2%; Sci-B-Vac: 40.0%).

Of the protocol deviations reported as related to procedures or tests, the majority in both treatment groups resulted from a delay or failure to collect vital signs or safety data. Approximately 1% of participants in each study group received the results of a hepatitis B antibody test that was completed at the study site before the end of the study. These 29 participants at UK Site 500 received the results of immunogenicity testing (seropositive or negative) conducted by a local laboratory before the end of the study because proof of seroprotection was required for employment. All 29 participants were seroprotected, so no additional vaccine doses were administered to these subjects. VBI did not exclude these participants from the PPS because their primary immunogenicity measure (antibody titer) was not revealed.

Thirty-one (4.4%) of Engerix-B and 98 (4.7%) Sci-B-Vac ITT subjects had at least one protocol deviations that led to exclusion from the PPS1. Subjects excluded from the PPS1 and PPS2 most frequently reported protocol deviations related to vaccine administration (Engerix-B: 47%; Sci-B-Vac: 43%).

**Reviewer's Comment:** *VBI appears to have omitted Sci-B-Vac participant* (b) (6) *from the protocol deviation count, possibly because this subject was missing the date and time for their only vaccine dose (Day 0). Regardless, this subject was excluded from the*

*PPS1 set. Two Engerix-B (* (b) (6) *) and three Sci-B-Vac participants (* (b) (6) *) had their baseline serology samples taken after vaccination according to the EC and IS datasets, but did not have corresponding protocol deviations, and thus were not flagged for exclusion from the PPS1 and PP2 datasets. Regardless, these subjects were excluded from the PPS1. Therefore, the primary immunogenicity analyses were not impacted.*

**Table 16.** Sci-B-Vac-002: Number (Percent) of Safety Set Participants by Disposition or Reason for Early Treatment or Study Discontinuation and Treatment Group or Overall

| Disposition | Engerix-B | Sci-B-Vac Lot A | Sci-B-Vac Lot B | Sci-B-Vac Lot C | Sci-B-Vac Total | Total |
|---|---|---|---|---|---|---|
| Randomized | 712 | 711 | 709 | 706 | 2126 | 2838 |
| Completed All Vaccinations | 671 (94.2) | 651 (91.6) | 662 (93.4) | 654 (92.6) | 1967 (92.5) | 2638 (93.0) |
| Discontinued from Vaccination | 41 (5.8) | 60 (8.4) | 47 (6.6) | 52 (7.4) | 159 (7.5) | 200 (7.0) |
| Completed Study | 643 (90.3) | 636 (89.5) | 637 (89.8) | 625 (88.5) | 1898 (89.3) | 2541 (89.5) |
| Early Withdrawal | 69 (9.7) | 75 (10.5) | 72 (10.2) | 81 (11.5) | 228 (10.7) | 297 (10.5) |
| **Primary Reason for Discontinuation*** | **Engerix-B** | **Sci-B-Vac Lot A** | **Sci-B-Vac Lot B** | **Sci-B-Vac Lot C** | **Sci-B-Vac Total** | **Total** |
| *Pregnancy* | 2 (0.3) | 3 (0.4) | 3 (0.4) | 5 (0.7) | 11 (0.5) | 13 (0.5) |
| *Non-serious AE* | 1 (0.1) | 3 (0.4) | 4 (0.6) | 2 (0.3) | 9 (0.4) | 10 (0.4) |
| *SAE* | 1 (0.1) | 2 (0.3) | 0 | 0 | 2 (0.1) | 3 (0.1) |
| *Other* | 36 (5.1) | 52 (7.3) | 40 (5.6) | 45 (6.4) | 137 (6.4) | 173 (6.1) |
| **Primary Reason for Early Withdrawal*** | **Engerix-B** | **Sci-B-Vac Lot A** | **Sci-B-Vac Lot B** | **Sci-B-Vac Lot C** | **Sci-B-Vac Total** | **Total** |
| *Lost to follow-up* | 48 (6.7) | 49 (6.9) | 51 (7.2) | 51 (7.2) | 151 (7.1) | 199 (7.0) |
| *Withdrew Consent (not caused by AE)* | 12 (1.7) | 15 (2.1) | 13 (1.8) | 17 (2.4) | 45 (2.1) | 57 (2.0) |
| *Pregnancy* | 1 (0.1) | 3 (0.4) | 2 (0.3) | 6 (0.8) | 11 (0.5) | 12 (0.4) |
| *Moved from Study Area* | 5 (0.7) | 3 (0.4) | 1 (0.1) | 3 (0.4) | 7 (0.3) | 12 (0.4) |
| *Non-serious AE* | 1 (0.1) | 2 (0.3) | 3 (0.4) | 1 (0.1) | 6 (0.3) | 7 (0.2) |
| *SAE* | 0 | 2 (0.3) | 0 | 0 | 2 (0.1) | 2 (0.1) |
| *Protocol Non-Compliance* | 0 | 0 | 1 (0.1) | 1 (0.1) | 2 (0.1) | 2 (0.1) |
| *Major Protocol Violation* | 0 | 0 | 0 | 2 (0.3) | 2 (0.1) | 2 (0.1) |
| *Regulatory Agency, Sponsor or PI Request* | 1 (0.1) | 0 | 0 | 0 | 0 | 1 (0.0) |
| *Investigator Decision* | 0 | 0 | 1 (0.1) | 0 | 1 (0.0) | 1 (0.0) |
| *Clinically Significant Change in Medical Condition* | 0 | 1 (0.1) | 0 | 0 | 1 (0.0) | 1 (0.0) |
| *Other* | 1 (0.1) | 0 | 0 | 0 | 0 | 1 (0.0) |

* AE: Adverse Event, PI: Principal Investigator, SAE: Serious Adverse Event
*Source: Adapted from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Table 15 (pp. 63–64).*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint

Table 17 shows the GMC results from Day 196 for the PPS1 Sci-B-Vac groups. The estimated GMCR with 95% CI for each pairwise comparison of the lots using the PPS1 are given in Table 18. All three pairwise comparisons met the pre-specified acceptance criterion for lot-to-lot consistency. Sensitivity analysis results using the FAS with and without baseline seropositive participants were consistent with these results.

**Table 17.** Sci-B-Vac-002: Summary Statistics* and Geometric Mean Concentrations (GMC) with 95% Confidence Intervals (CI) for Per-Protocol Set 1 Concentrations at 4 Weeks After the Third Vaccine Dose by Sci-B-Vac Lot

| Statistic | Sci-B-Vac Lot A | Sci-B-Vac Lot B | Sci-B-Vac Lot C |
|---|---|---|---|
| Number of Subjects | 611 | 610 | 619 |
| Median | 12200 | 10700 | 12000 |
| Min, Max | 2.1, 20000 | 2.1, 20000 | 2.1, 20000 |
| Estimated GMC | 5882.25 | 4821.65 | 5569.89 |
| 95% CI | 5112.43, 6767.99 | 4190.10, 5548.39 | 4844.63, 6403.73 |

*Summary statistics calculated on the logarithmic scale and presented on the original scale.*
*Source: Adapted from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Table 21 (p. 74).*

**Table 18.** Sci-B-Vac-002: Per-Protocol Set 1 Lot-to-Lot Comparisons

| Lot-to-Lot Comparison | Adjusted GMC Ratio (95% CI) |
|---|---|
| B/A | 0.82 (0.67, 1.00) |
| C/A | 0.95 (0.78, 1.15) |
| C/B | 1.16 (0.95, 1.41) |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Table 21 (p. 74).*

**Reviewer's Comment:** *I have verified the primary endpoint analyses, although using both the IS and ADIS datasets, I find slightly different adjusted GMC ratios (95% CIs) for C/A of 0.94 (0.77, 1.14) and C/B of 1.14 (0.93, 1.40). I have also verified the sensitivity analyses and that the primary lot-to-lot consistency results are similar using the ITT.*

6.2.11.2 Analyses of Secondary Endpoint

Table 19 shows the seroprotection results at Day 196 for the combined Sci-B-Vac groups and Engerix-B using the PPS2. The estimated difference in SPRs in the PPS2 was 4.49% (95% CI: 2.90%, 6.63%), which met the pre-specified non-inferiority criterion. Sensitivity results using the FAS and ITT with and without baseline seropositive participants were similar.

**Table 19.** Sci-B-Vac-002: Per-Protocol Set 2 Seroprotection Rates (SPR) at 4 Weeks After the Third Vaccine Dose by Vaccine Group with 95% Confidence Intervals (CI)

| Statistic | Engerix-B | Sci-B-Vac |
|---|---|---|
| Evaluated Participants | 592 | 1753 |
| Seroprotected Participants | 561 | 1740 |
| Seroprotection Rate (SPR) | 94.76% | 99.26% |
| SPR 95% CI | 92.65%, 96.41% | 98.74%, 99.60% |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Table 22 (p. 75)*

**Reviewer's Comment:** *I have verified the secondary endpoint analyses, including the sensitivity analyses.*

6.2.11.3 Subpopulation Analyses

Table 20 shows the seroprotection rates at Day 196 with 95% CIs for each treatment group, along with the differences in seroprotection rates between treatment groups and 95% CIs, in the PPS2 for important subpopulations. Seroprotection rates in the Sci-B-Vac group were similar across all subgroups and consistent with the overall seroprotection rate. Seroprotection rates in the Engerix-B group were lower among participants who were Hispanic, had a BMI ≥ 30, drank on average 2–3 drinks per day, or were a current smoker, compared to other subpopulations and the overall seroprotection rate. Therefore, the difference in seroprotection rates was higher among these groups compared to the other subgroups and the overall difference in seroprotection rates. Participants from the US tended to have lower seroprotection rates relative to European and Canadian participants; US participants were also more likely to be Hispanic compared to European and Canadian participants and were older and with higher BMIs than European participants.

**Table 20.** Sci-B-Vac-002: Per-Protocol Set 2 Subgroup Seroprotection Rates (SPR) with 95% Confidence Intervals (CI) by Treatment Group and Seroprotection Rate Differences with 95% CI

| Subgroup | Engerix-B: Freq. | Engerix-B: SPR (95% CI) | Sci-B-Vac: Freq. | Sci-B-Vac: SPR (95% CI) | SPR Difference (95% CI) |
|---|---|---|---|---|---|
| **Gender** | - | - | - | - | - |
| Men | 225/241 | 93.4 (89.4, 96.2) | 732/737 | 99.3 (98.4, 99.8) | 6.0 (3.3, 9.9) |
| Women | 336/351 | 95.7 (93.0, 97.6) | 1008/1016 | 99.2 (98.5, 99.7) | 3.5 (1.7, 6.2) |
| **Race** | - | - | - | - | - |
| White | 520/550 | 94.5 (92.3, 96.3) | 1618/1631 | 99.2 (98.6, 99.6) | 4.7 (3.0, 6.9) |
| Black or African American | 27/27 | 100 (87.2, 100) | 82/82 | 100 (95.6, 100) | 0 (-4.51, 12.6) |
| Other | 14/15 | 93.3 (68.1, 99.8) | 40/40 | 100 (91.2, 100) | 6.7 (-2.7, 30.1) |
| **Ethnicity** | - | - | - | - | - |
| Hispanic/Latino | 49/54 | 90.7 (79.7, 96.9) | 139/139 | 100 (97.4, 100) | 9.3 (4.0, 19.9) |
| Non-Hispanic./Latino | 510/536 | 95.1 (93.0, 96.8) | 1596/1609 | 99.2 (98.6, 99.6) | 4.0 (2.4, 6.2) |
| **Region** | - | - | - | - | - |
| United States | 125/138 | 90.6 (84.4, 94.9) | 400/405 | 98.8 (97.1, 99.6) | 8.2 (4.1, 14.3) |
| Canada | 21/22 | 95.5 (77.2, 99.9) | 76/77 | 98.7 (93.0, 100) | 3.3 (-3.4, 20.7) |
| Europe | 415/432 | 96.1 (93.8, 97.7) | 1264/1271 | 99.4 (98.9, 99.8) | 3.4 (1.8, 5.7) |
| **BMI (kg/m2)** | - | - | - | - | - |
| >30 | 80/91 | 87.9 (79.4, 93.8) | 314/315 | 99.7 (98.2, 100) | 11.8 (6.5, 20.1) |
| ≤30 | 481/501 | 96.0 (93.9, 97.5) | 1426/1438 | 99.2 (98.5, 99.6) | 3.2 (1.7, 5.3) |
| **Alcohol Consumption** | - | - | - | - | - |
| ≥4 Drinks | 4/4 | 100 (39.8, 100) | 8/8 | 100 (63.1, 100) | 0 (-34.4, 51.2) |
| 2-3 Drinks | 38/42 | 90.5 (77.4, 97.3) | 103/103 | 100 (96.5, 100) | 9.5 (3.8, 22.1) |
| 0-1 Drink | 519/546 | 95.1 (92.9, 96.7) | 1629/1642 | 99.2 (98.6, 99.6) | 4.2 (2.6, 6.3) |
| **Smoking Status** | - | - | - | - | - |
| Current Smoker | 88/100 | 88.0 (80.0, 93.6) | 312/316 | 98.7 (96.8, 99.7) | 10.7 (5.5, 18.6) |
| Past Smoker | 113/119 | 95.0 (89.3, 98.1) | 342/346 | 98.8 (97.1, 99.7) | 3.9 (0.7, 9.5) |
| Non-smoker | 360/373 | 96.5 (94.1, 98.1) | 1085/1090 | 99.5 (98.9, 99.9) | 3.0 (1.5, 5.4) |

| Subgroup | Engerix-B: Freq. | Engerix-B: SPR (95% CI) | Sci-B-Vac: Freq. | Sci-B-Vac: SPR (95% CI) | SPR Difference (95% CI) |
|---|---|---|---|---|---|
| **Non-Study Vaccine** | | | | | |
| No Vaccine | 459/486 | 94.4 (92.0, 96.3) | 1445/1458 | 99.1 (98.5, 99.5) | 4.7 (2.9, 7.1) |
| Vaccine | 102/106 | 96.2 (90.6, 99.0) | 295/295 | 100 (98.8, 100) | 3.8 (1.5, 9.3) |

*Source: Created from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report Table 23 (pp. 76–77) and Figure 3 (p. 78).*

**Reviewer's Comment:** *The subpopulation results should be interpreted cautiously as some subgroups were too small to yield precise estimates of the vaccine efficacy or adequate power for hypothesis testing, and subgroup hypothesis tests performed by the applicant were neither pre-specified nor adjusted for multiplicity. Overall, the subgroup analysis do not suggest any obviously inconsistent trends in vaccine efficacy for these subgroups.*

6.2.11.5 Exploratory and Post Hoc Analyses

A total of 46 Asian participants enrolled in the trial, with 44 participants included in the PPS and 36 in the PPS2. Asian participants were slightly more likely to receive Sci-B-Vac Lots B and C, compared to the overall study population. Safety Set Asian participants in both vaccine groups tended to be slightly younger, to have lower BMIs, to be non-smokers, to consume 0–1 alcoholic drinks per day, and to be Canadian, compared to the overall study population. There was some imbalance in gender across the vaccine groups, probably because of the small sample size: 56% of Engerix-B and 32% of Sci-B-Vac participants were females. No Asian participants reported consuming more than 0–1 alcoholic drinks per day. PPS1 and PPS2 demographics were similar for Asian participants.

Table 21 shows the results of the post-hoc descriptive immunogenicity analyses in the PPS2 for the Asian subgroup and the overall vaccine groups, for comparison. While mean GMCs and the percent of participants with titers ≥ 100 mIU/mL were lower at Days 168, 196, and 336 for the Sci-B-Vac Asian subgroup compared to the overall Sci-B-Vac group, seroprotection rates and percent of non-responders at Day 196 were comparable. Results for the PPS and FAS were not substantially different, although GMCs in both of these analysis sets tended to be slightly lower than those in the PPS2.

**Reviewer's Comment:** *I have verified these results and the results in Table 21. Given the very small number of participants, these results should be interpreted cautiously, as they are subject to substantial uncertainty.*

**Table 21.** Sci-B-Vac-002: Post-Hoc Immunogenicity Analysis of Per-Protocol Set 2 Asian Subgroup

| Statistic* | Engerix-B: Asian | Sci-B-Vac: Asian | Engerix-B: Overall | Sci-B-Vac: Overall |
|---|---|---|---|---|
| Mean GMCs | | | | |
| *Day 168* | 19.64 | 96.00 | 14.99 | 118.95 |
| *Day 196* | 7530.33 | 3904.54 | 1526.26 | 5443.07 |
| *Day 336* | 1287.88 | 1151.43 | 473.02 | 2093.80 |
| SPRs | | | | |
| *Day 168* | 50.0% | 75.0% | 51.58% | 90.42% |
| *Day 196* | 100% | 100% | 94.76% | 99.26% |
| *Day 336* | 87.5% | 100% | 92.76% | 98.66% |
| % ≥ 100 mIU/mL | | | | |
| *Day 168* | 25.0% | 53.6% | 16.58% | 55.27% |
| *Day 196* | 100% | 93% | 86.32% | 95.78% |
| *Day 336* | 75.0% | 85% | 73.97% | 92.67% |
| % Non-Responders (Day 196) | 0% | 0% | 5.24% | 0.74% |

*\*GMC: geometric mean concentration; SPRs: seroprotection rates.*
*Source: Created from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Section 11.3.2, Section 14, Table 14.2.2.6a, Table 14.2.3.1, Table 14.2.3.3a, Table 14.2.4.1, Table 14.2.4.4a, Table 14.2.5.3, and Table 14.2.5.4.*

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety data for Sci-B-Vac-002 were collected as for Sci-B-Vac-001. See Section 6.1.12.1 for details.

6.2.12.2 Deaths

One death was reported. Participant (b) (6) , a Black or African American male aged 35 years old who received Sci-B-Vac Lot A, experienced sudden cardiac death (b) (6) days after the first vaccine dose. Participant (b) (6) had a history of open-heart surgery and hypertrophic heart disease. The death was assessed as unrelated to treatment by investigator.

6.2.12.3 Nonfatal Serious Adverse Events

A total of 51 SAEs were reported by a total of 45 participants. Of them, 42 (2.0%) Sci-B-Vac participants reported 47 SAEs, and 3 (0.4%) Engerix-B participants reported 4 SAEs. Appendicitis and intervertebral disc protrusion were reported in 3 participants each in the Sci-B-Vac group, and erysipelas was reported in 2 Sci-B-Vac participants. All other SAEs were reported by only one participant. One grade 1 SAE, ankyloglossia congenital, was reported in the offspring of a Sci-B-Vac study participant and was considered by the site investigator as possibly related to vaccination. All other SAEs were not considered related to study vaccine.

Please refer to the clinical review for a detailed discussion of SAEs.

**Reviewer's Comment:** *I have verified the results described in Sections 6.2.12.2 and 6.2.12.3.*

6.2.12.4 Solicited Adverse Events

Solicited local AEs were reported by 469 (65.9%) Engerix-B and 1,805 (85.0%) Sci-B-Vac participants. Table 22 shows the frequency of solicited local AEs by vaccine group. Injection site pain and tenderness were the most frequently reported solicited local AEs in both vaccine groups. Rates of participants reporting specific local solicited AEs were higher for Sci-B-Vac compared to Engerix-B for all solicited local AEs. Rates of participants reporting specific solicited local AEs after each dose were consistent with the overall rates, though lower, and relatively consistent across doses. Rates of participants reporting specific solicited local AEs after each dose were higher for Sci-B-Vac compared to Engerix-B.

**Table 22.** Sci-B-Vac-002: Number (Percent) of Participants Reporting Specific Solicited Local Adverse Events in the 7 Days After Any Vaccine Dose by Vaccine Group

| Adverse Event | Engerix-B | Sci-B-Vac |
|---|---|---|
| Pain | 384 (53.9) | 1605 (75.6) |
| Tenderness | 391 (54.9) | 1595 (75.1) |
| Itching | 88 (12.4) | 281 (13.2) |
| Redness | 12 (1.7) | 61 (2.9) |
| Swelling | 6 (0.8) | 55 (2.6) |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Table 36 (p. 98).*

Rates of participants reporting grades 3 and 4 solicited local AEs were somewhat higher for Sci-B-Vac. Eight (1.1%) Engerix-B participants and 61 (2.9%) Sci-B-Vac participants reported grade 3 solicited, local AEs with pain and tenderness most frequently reported. Two (0.3%) Engerix-B participants and 11 (0.5%) Sci-B-Vac participants reported grade 4 AEs. All grade 4 AEs were edema or erythema. Two Sci-B-Vac participants reported grade 4 edema. Two (0.3%) Engerix-B and nine (0.4%) Sci-B-Vac participants reported grade 4 erythema. VBI noted that in all these cases, the reaction was graded "potentially life-threatening" because of self-reported skin necrosis at the injection site and that the erythema or swelling would otherwise have been grade 1 events. The majority of solicited local AEs occurred within 1 to 3 days after vaccination and lasted a median of 1 to 2 days for both vaccines.

Solicited systemic AEs were reported by 428 (60.1%) Engerix-B and 1,445 (68.0%) Sci-B-Vac participants. Table 23 shows the frequency of solicited systemic AEs by vaccine group. The most frequently reported solicited systemic AEs were fatigue, headache, and myalgia. Rates of participants reporting specific solicited systemic AEs were similar across vaccine groups, except for myalgia, which was reported more frequently by Sci-B-Vac participants. Rates of participants reporting specific solicited systemic AEs after

each dose were consistent with the overall rates, with higher rates reported after the first dose for both vaccines.

**Table 23.** Sci-B-Vac-002: Number (Percent) of Participants Reporting Specific Solicited Systemic Adverse Events in the 7 Days After Any Vaccine Dose by Vaccine Group

| Adverse Event | Engerix-B | Sci-B-Vac |
|---|---|---|
| Fatigue | 284 (39.9) | 852 (40.1) |
| Headache | 268 (37.6) | 811 (38.2) |
| Myalgia | 231 (32.4) | 942 (44.4) |
| Diarrhea | 105 (14.7) | 277 (13.0) |
| Nausea/Vomiting | 86 (12.1) | 251 (11.8) |

*Source: Adapted from BLA 125737/0, Sci-B-Vac-002 Clinical Study Report, Table 40 (p. 103).*

Rates of participants reporting grades 3 and 4 solicited local AEs were similar between the two vaccines, though higher for Sci-B-Vac. Twenty-one (2.9%) Engerix-B participants and 68 (3.2%) Sci-B-Vac participants reported grade 3 solicited, systemic AEs with fatigue, headache, and myalgia most frequently reported. No Engerix-B participants and two (0.1%) Sci-B-Vac participants reported grade 4 AEs. One participant reported grade 4 headache after the third dose, which was assessed as unlikely to be related to study vaccine by investigator, and the other participant reported grade 4 nausea and vomiting after the third dose, as part of an episode of vertigo, which was assessed as unrelated to the vaccine by investigator. The majority of solicited systemic AEs onset within 1 to 4 days after vaccination, and solicited systemic AEs lasted a median of 1 to 2 days for both vaccines.

Solicited other AEs were reported by 274 (38.7%) Engerix-B participants and 822 (38.5%) Sci-B-Vac participants. Bradycardia, hypertension, and increased/decreased respiratory rate were the most frequently reported solicited other AEs in both vaccine groups. Rates of participants reporting specific solicited other AEs were similar across the two vaccine groups.

The majority of solicited other AEs were grade 1 or 2, and rates of participants reporting events by severity were similar for the two vaccines. Bradycardia, diastolic hypertension, and systolic hypertension were the most frequently reported grade 3 solicited other AEs in both vaccine groups. One grade 4 fever was reported on Day 2 after the 3rd Sci-B-Vac vaccination.

Solicited AEs that lasted beyond Day 7 were reported by 54 (7.6%) Engerix-B and 186 (8.8%) Sci-B-Vac participants. The most frequent solicited AEs that lasted beyond Day 7 were fatigue, injection site pain, headache, and myalgia. Most solicited AEs that lasted beyond Day 7 were mild or moderate in severity. Five (0.7%) Engerix-B and 22 (1.0%) Sci-B-Vac participants reported grade 3 solicited AEs that lasted beyond 7 days. No grade 4 events lasted beyond 7 days.

**Reviewer's Comment:** *I have verified most key results described in Section 6.2.12.4, of this document, as well as the results in Tables 36–39 of the Sci-B-Vac-002 Report.*

*I found 2 Sci-B-Vac participants reporting grade 4 fevers: the participant described above and Participant* (b) (6) *, who reported a grade 4 fever on Day 1 within 30 minutes of their first vaccination.*

6.2.12.5 Unsolicited Adverse Events

Within 28 days of any vaccine dose, 348 (48.9%) Engerix-B and 1042 (49.1%) Sci-B-Vac participants reported at least one unsolicited AE. Rates of participants reporting at least 1 unsolicited AE for AEs reported by at least 1% of each vaccine group were similar by system organ class and preferred term. The most common unsolicited AEs in both vaccine groups were infections and infestations, specifically upper respiratory tract infections and nasopharyngitis, though headache was the most frequently reported AE. Other frequently reported unsolicited AEs included dysmenorrhea, fatigue, and oropharyngeal pain. Results were generally similar for rates of participants reporting at least 1 unsolicited AE through the end of the study.

The majority of participants with unsolicited AEs reported within 28 days of any vaccination were mild or moderate in severity. Grade 3 unsolicited AEs within 28 days of any vaccination were reported by 33 (4.6%) Engerix-B and 135 (6.4%) Sci-B-Vac participants. Grade 4 unsolicited AEs within 28 days of any vaccination were reported by one (0.1%) Engerix-B and four (0.2%) Sci-B-Vac participants.

Rates of vaccine-related unsolicited AEs within 28 days after any vaccination were similar, with 98 (13.8%) Engerix-B and 322 (15.2%) Sci-B-Vac participants reporting vaccine-related unsolicited AEs. The most common vaccine-related unsolicited AEs were fatigue, injection site pain, and headache; many were solicited AEs that continued beyond Day 7. Excluding solicited AEs that continued beyond Day 7, the most common vaccine-related unsolicited AEs were upper respiratory infection, dizziness, headache, and injection site bruising. Seven (1.0%) Engerix-B and 23 (1.1%) Sci-B-Vac participants reported grade 3, vaccine-related events. No vaccine-related, unsolicited grade 3 AE was reported by more than one Engerix-B participant. Sci-B-Vac participants most frequently reported fatigue, injection site pain, headache, and myalgia.

**Reviewer's Comment:** *I have verified the results described in Section 6.2.12.5 and in Tables 49 and 50 (pp. 117–120) of the Sci-B-Vac-002 Report.*

6.2.12.6 Clinical Test Results
Please refer to the clinical review.

6.2.12.7 Dropouts and/or Discontinuations
A total of 13 participants withdrew from treatment because of AEs including 2 Engerix-B and 11 Sci-B-Vac participants. Dizziness, reported by 2 participants, was the only AE leading to treatment discontinuation that was reported by more than one participant. A

total of 9 participants discontinued the study because of an AE including 8 Sci-B-Vac and 1 Engerix-B participant.

**Reviewer's Comment:** *I verified these results.*

## 7. INTEGRATED OVERVIEW OF EFFICACY

No pooled efficacy analysis of Sci-B-Vac-001 and Sci-B-Vac-002 was planned.

## 8. INTEGRATED OVERVIEW OF SAFETY

### 8.1 Safety Assessment Methods

Please refer to Section 6 for a brief description of the safety data collection methods from Sci-B-Vac-001 and Sci-B-Vac-002 and to the clinical review for more details. The pre-specified integrated summary of safety (ISS) used the same descriptive analyses as described in Section 6 for the individual studies.

**Reviewer's Comment:** *Because Sci-B-Vac-001 and Sci-B-Vac-002 had similar safety results and only 1 death was observed across both studies, the ISS reactogenicity, non-serious AE, and death results were similar to the individual studies' results. Therefore, this section focuses on the non-fatal SAE and AESI results, where the increased safety database may provide additional information about rare AEs.*

### 8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Both Sci-B-Vac-001 and Sci-B-Vac-002 were included in the safety analysis for the ISS. Please refer to Section 5.3, Table 1, as well as Section 6, for a description of these two studies.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The integrated summary of safety used the combined safety sets from the two pivotal trials (referred to as the Integrated Safety Set). In the Integrated Safety Set (ISS), 1,523 participants were randomized to Engerix-B and 2,922 participants were randomized to Sci-B-Vac. A majority of participants completed their assigned vaccination series (Engerix-B: 95.6%; Sci-B-Vac: 93.3%).

Table 24 shows the demographics of the ISS. The two treatment groups generally had similar demographics, with slightly more female, younger, and lower BMI participants in the Sci-B-Vac group. The pooled demographics for each treatment group were similar to the corresponding demographics from each individual study, except for age and BMI. Participants in the pooled set were on average younger and had a lower BMI than the

participants in Sci-B-Vac-001 study and had a higher BMI than participants in the Sci-B-Vac-002 study, because of the populations recruited for each of the studies.

**Table 24.** Integrated Summary of Safety: Demographics by Treatment Group

| Demographic* | Engerix-B | Sci-B-Vac |
|---|---|---|
| Gender, # (%) | - | - |
| *Male* | 594 (39.0) | 1222 (41.8) |
| *Female* | 929 (61.0) | 1698 (58.2) |
| Race, # (%) | - | - |
| *White* | 1384 (90.9) | 1941 (91.4) |
| *Asian* | 13 (0.9) | 45 (1.5) |
| *Black or African American* | 103 (6.8) | 189 (6.5) |
| *American Indian or Alaska Native* | 6 (0.4) | 11 (0.4) |
| *Native Hawaiian or Pacific Islander* | 0 (0.0) | 1 (< 0.1) |
| *Other* | 17 (1.1) | 18 (0.6) |
| Ethnicity, # (%) | - | - |
| *Hispanic or Latino* | 149 (9.8) | 274 (9.4) |
| *Non-Hispanic or Latino* | 1368 (89.8) | 2638 (90.3) |
| *Not Collected* | 6 (0.4) | 8 (0.3) |
| Age (years) | - | - |
| *Mean (SD)* | 45.8 (16.15) | 39.8 (14.10) |
| *Median* | 43.0 | 38.0 |
| *Min, Max* | 18, 90 | 18, 86 |
| BMI (kg/m$_2$) | - | - |
| *Mean (SD)* | 27.5 (5.70) | 26.8 (5.18) |
| *Median* | 26.7 | 26.1 |
| *Min, Max* | 11.3, 63.5 | 13.5, 56.3 |
| BMI Category (kg/m2) , # (%) | - | - |
| ≤30 | 1114 (73.1) | 2236 (76.6) |
| >30 | 409 (26.9) | 684 (23.4) |
| Diabetes Status | - | - |
| *Diabetic* | 65 (4.3) | 61 (2.1) |
| *Non-Diabetic* | 1458 (95.7) | 2859 (97.9) |
| Smoking Status/Tobacco use, # (%) | - | - |
| *Current user* | 249 (16.3) | 510 (17.5) |
| *Former user* | 365 (24.0) | 607 (20.8) |
| *Non-user* | 909 (59.7) | 1802 (61.7) |
| Average Daily Alcohol Consumption, # (%) | - | - |
| *0-1 drink* | 1397 (91.7) | 2752 (93.3) |
| *2-3 drinks* | 117 (7.7) | 179 (6.1) |
| *≥ 4 drinks* | 9 (0.6) | 16 (0.5) |
| Country/Region, # (%) | - | - |
| *United States* | 530 (34.8) | 900 (30.8) |

| Demographic* | Engerix-B | Sci-B-Vac |
|---|---|---|
| *Canada* | 164 (10.8) | 216 (7.4) |
| *Europe* | 829 (54.4) | 1472 (61.8) |

*Source: Adapted from BLA 125737/0 Module 2, Section 2.7.4, Integrated Summary of Safety, Table 10 (p. 35).*

## 8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

While both studies are similar, there are several key differences that could impact the interpretation of the ISS results:
- Population: Sci-B-Vac-001 enrolled adults aged 18 years old and older who had stable chronic conditions, while Sci-B-Vac-002 only enrolled healthy adults aged 18 to 45 years old.
- Randomization: Sci-B-Vac-001 used stratified randomization by age group, while Sci-B-Vac-002 did not.

**Reviewer's Comment:** *The clinical reviewer identified several discrepancies between Sci-B-Vac-001 and Sci-B-Vac-002 in the coding of the same AE verbatim terms which resulted in different system organ classes and preferred terms (AEDECOD). These differences persisted in the ISS datasets. In the response to an information request (BLA 125737/0.5), VBI clarified that the same MedDRA version (20.1) was used for both studies and that the coding of AEs was consistent within each study. However, VBI did not assess the consistency of coding across the two studies. Inconsistent coding of AEs across studies may result in estimates of AE preferred term rates from the Integrated Summary of Safety that do not reflect the true preferred term rates across both studies.*

## 8.4 Safety Results

### 8.4.1 Deaths

Across Sci-B-Vac-001 and Sci-B-Vac-002, one death occurred in Sci-B-Vac-002. Please refer to Section 6.2.12.2 for details.

### 8.4.2 Nonfatal Serious Adverse Events

In the ISS, 24 (1.6%) Engerix-B and 74 (2.5%) Sci-B-Vac participants reported one or more non-fatal SAE through the end of the study. Nine (0.6%) Engerix-B and 25 (0.9%) Sci-B-Vac participants reported one or more non-fatal SAE in the 28 days after any vaccine dose.

Through the end of the studies, atrial fibrillation and colon cancer were the only SAEs reported by more than one Engerix-B participant. Appendicitis, intervertebral disc protrusion, ankle fracture, back pain, congestive heart failure, vertigo, erysipelas,

pneumonia, joint dislocation, tendon rupture, and syncope were all reported by more than one Sci-B-Vac participant through the end of the studies.

Appendicitis, vertigo, joint dislocation were all reported by 2 or more Sci-B-Vac participants within 28 days of vaccination. No SAE was reported by more than one Engerix-B participant within 28 days of vaccination.

Ten Sci-B-Vac participants reported 1 SAE each within 7 days of any vaccination. The only SAE reported by more than 1 participant within 7 days was vertigo.

**Reviewer's Comment:** *I have confirmed most of the results described in Section 8.4.2. Besides the SAEs given above, I found two Engerix-B participants reporting nephrolithiasis and two Engerix-B participants reporting urinary tract infection through the end of the study. I also found two Sci-B-Vac participants reporting alcoholic liver disease within 28 days of vaccination.*

*SAEs occurring in more than one participant, but which were not identified in Sci-B-Vac-001 or Sci-B-Vac-002 include: ankle fracture, back pain, vertigo, pneumonia, joint dislocation, tendon rupture, syncope, alcoholic liver disease, nephrolithiasis, and urinary tract infection.*

8.4.3 Common Adverse Events

In the ISS, 48.4% of Engerix-B and 48.3% of Sci-B-Vac participants reported AEs within 28 days of any vaccination. The most frequently reported AEs within 28 days of any vaccination included headache, upper respiratory tract infection, nasopharyngitis, fatigue, dysmenorrhea, back pain, myalgia, oropharyngeal pain, and injection site pain. The frequencies of these AEs in the two treatment groups were similar. When solicited AEs lasting beyond Day 7 were excluded, the most frequently reported AEs within 28 days included headache, upper respiratory tract infection, dysmenorrhea, and injection site pain.

In the ISS, 12.9% of Engerix-B and 15.2% of Sci-B-Vac participants reported AEs considered vaccine-related (very likely, probably, or possibly related) within 28 days after any vaccination. The most frequently reported such AEs were fatigue, injection site pain, and headache. When solicited AEs that persisted beyond Day 7 were excluded, the most frequently reported vaccine-related AEs were upper respiratory tract infection, dizziness, injection site bruising, oropharyngeal pain, nasopharyngitis, and headache. These results were consistent with the results from the individual studies.

Please refer to the clinical review for further details.

**Reviewer's Comment:** *I have verified the results described in Section 8.4.3.*

8.4.4 Systemic Adverse Events

In the ISS, solicited systemic AEs within 7 days of any vaccination were reported by 54.1% of Engerix-B participants and 64.7% of Sci-B-Vac participants. Sci-B-Vac participants were more likely to report myalgia (Engerix-B: 28.1%; Sci-B-Vac: 41.7%). The incidence of local reactogenicity tended to decrease after the second vaccination, and most participants reported mild or moderate solicited AEs. Three (0.1%) Sci-B-Vac participants reported grade 4 solicited systemic AEs of fatigue, nausea/vomiting, and headache. These results were consistent with those from the individual studies.

Please refer to the clinical review for further details.

8.4.5 Local Reactogenicity

In the ISS, solicited local AEs within 7 days of any vaccination were reported by 55.7% of Engerix-B participants and 81.4% of Sci-B-Vac participants. Sci-B-Vac participants were much more likely to report injection site pain (Engerix-B: 44.5%; Sci-B-Vac: 72.2%) and tenderness (Engerix-B: 44.2%; Sci-B-Vac: 71.2%). The incidence of local reactogenicity decreased after the second vaccination, and most participants reported mild or moderate reactogenicity. Ten (0.7%) Engerix-B and 14 (0.5%) Sci-B-Vac participants reported grade 4 solicited local AEs. These AEs were swelling or redness, and most were not medically attended. These results were consistent with those from the individual studies.

Please refer to the clinical review for further details.

**Reviewer's Comment:** *I have verified the results described in Section 8.4.4 and 8.4.5.*

8.4.6 Clinical Test Results

Please refer to the clinical review.

8.4.7 Study Dropouts/Discontinuations

Discontinuation of treatment caused by non-serious and serious AEs was uncommon, occurring in no more than 0.4% of participants in either treatment group. Slightly more Sci-B-Vac participants became pregnant (0.5%) than Engerix-B participants (0.1%). In the ISS, most participants completed the study, with 111 (7.29%) Engerix-B and 266 (9.11%) Sci-B-Vac participants discontinuing the study early. Discontinuation of the study caused by non-serious and serious AEs was uncommon, occurring in no more than 0.3% of participants in each treatment group.

**Reviewer's Comment:** *I have verified the results described in Section 8.4.7.*

## 8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Please refer to the clinical review.

8.5.2 Time Dependency for Adverse Events

Please refer to the clinical review.

## 8.6 Safety Conclusions

The results of the integrated summary of safety were consistent with the safety results from the individual studies. The rates of solicited AEs in the combined safety set were similar to the rates in the individual studies, and the rates of commonly reported unsolicited AEs were similar to the rates in the individual studies.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

Sci-B-Vac-001 met the pre-specified non-inferiority criteria for the primary endpoint of seroprotection rates to Engerix-B, with seroprotection rates of 76.5% for Engerix-B and 91.4% for Sci-B-Vac, yielding a difference in seroprotection rates of 14.88% (95% CI: 11.18%, 18.63%). Sci-B-Vac-002 met the pre-specified lot-to-lot consistency criteria for the three lots of Sci-B-Vac and demonstrated non-inferiority of seroprotection rates to Engerix-B, with seroprotection rates of 94.8% for Engerix-B and 99.3% for Sci-B-Vac, yielding a difference in seroprotection rates of 4.49% (95% CI: 2.90%, 6.63%). Subgroup results in both studies were consistent to the overall results, except for participants who consume four or more alcoholic drinks per day, probably because of the very few participants who consume four or more alcoholic drinks per day, which limits the interpretation of the results in this subgroup.

Across both pivotal studies, 48.4% of Engerix-B and 48.3% of Sci-B-Vac participants reported AEs within 28 days of any vaccination and 24 (1.6%) Engerix-B and 74 (2.5%) Sci-B-Vac participants reported one or more non-fatal SAE through the end of the study. One death, considered unrelated to study vaccine, was reported in the Sci-B-Vac group. In addition, 12.9% of Engerix-B and 15.2% of Sci-B-Vac participants reported AEs considered vaccine-related, with the most frequently reported vaccine-related AEs including fatigue, injection site pain, and headache. Sci-B-Vac participants were more likely to report injection site pain (Engerix-B: 44.5%, Sci-B-Vac: 72.2%), injection site tenderness (Engerix-B: 44.2%, Sci-B-Vac: 71.2%), and myalgia (Engerix-B: 28.1%, Sci-B-Vac: 41.7%).

## 10.2 Conclusions and Recommendations

In general, there were no major statistical issues identified in this submission, and I verified the primary immunogenicity and lot-to-lot consistency results. The primary efficacy results, non-inferiority of immunogenicity compared to Engerix-B, met the pre-specified success criteria and support the approval of Prehevbrio. I defer to the clinical to assess the regulatory significance of the safety results, given the relatively higher rates of solicited AEs reported by the Sci-B-Vac participants and inconsistent coding of AEs between the two studies.