BLA Clinical Review Memorandum

Application Type	Original BLA
STN	125737.0
CBER Received Date	November 30, 2020
PDUFA Goal Date	November 30, 2021
Division / Office	CRB2/DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Darcie Everett, MD, MPH
Review Completion Date / Stamped Date	
Supervisory Concurrence	Meghan Ferris, MD, MPH, Team Lead Andrea Hulse, MD, CRB2 Chief
Applicant	VBI Vaccines (Delaware) Inc.
Established Name	Sci-B-Vac
(Proposed) Trade Name	Prehevbrio
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	10 mcg recombinant hepatitis B surface antigens (pre-S1, pre-S2, and S) adsorbed on aluminum hydroxide adjuvant (0.5 mg/mL)
Dosage Form(s) and Route(s) of Administration	1 mL injectable suspension for intramuscular use supplied as a single-dose vial
Dosing Regimen	A series of three doses on a 0-,1-, and 6-month schedule
Indication(s) and Intended Population(s)	For prevention of infection caused by all known subtypes of the hepatitis B virus in adults, age ≥18 years old
Orphan Designated (Yes/No)	No

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GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
$Al(OH)_3$	aluminum hydroxide
ALT	alanine transaminase
ANCOVA	analysis of covariance
anti-HBs	hepatitis B surface antibody
AP	alkaline phosphatase
AST	aspartate transaminase
BLA	Biologics License Application
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
DART	developmental and reproductive toxicity
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DVRPA	Division of Vaccines and Related Products Applications
DVT	deep vein thrombosis
eCRF	electronic case report form
EOP2	end of phase 2
ER	emergency room
FAS	Full Analysis Set
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl-transferase
GLP	good laboratory practice
GMC	geometric mean concentration
GMR	geometric mean ratio
GSK	GlaxoSmithKline
HBA1C	hemoglobin A1C
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HLGT	higher level group term
HLT	higher level term
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon
IND	investigational new drug
ILI	influenza-like illness
IM	intramuscular
iPSP	initial pediatric study plan
IR	information request

IS	injection site
ISS	integrated summary of safety
ITT	intent-to-treat
LB	lower bound
LMP	last menstrual period
LLOQ	lower limit of quantitation
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MM	medical monitor
NOCI	new-onset chronic illness
OVRR	Office of Vaccines Research and Review
PeRC	Pediatric Review Committee
PMR	Polymyalgia rheumatica
PPS	Per Protocol Set
PREA	Pediatric Research Equity Act
PT	Preferred Term
PV	pharmacovigilance
PVP	pharmacovigilance plan
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPR	seroprotective rate
SSA	Clinical Laboratory Sub-Study Analysis (Set)
US	United States
V	Visit
WBC	white blood cell
YOA	years of age

1. EXECUTIVE SUMMARY

The Applicant, VBI Vaccines Inc., submitted BLA 125737 to the Center for Biologics Evaluation and Research (CBER) to support licensure of Prehevbrio, a recombinant hepatitis B subunit vaccine with aluminum hydroxide adjuvant, for the prevention of infection caused by all known subtypes of hepatitis B virus (HBV) in adults ≥18 years of age (YOA). Prehevbrio, hereafter referred to as Sci-B-Vac, contains the three envelope proteins of HBV—Pre-S1 (large), Pre-S2 (medium), and S (small) hepatitis B surface antigens (HBsAg)—produced by expression in Chinese hamster ovary (CHO) cells. Sci-B-Vac is administered intramuscularly as a three-dose regimen of 1.0 mL at Months 0, 1, and 6. Sci-B-Vac initially received marketing authorization in Israel in 2000 and subsequently in other countries in Asia, Africa, and South America.

HBV infection can cause an acute or chronic inflammation of the liver, which can lead to cirrhosis, liver cancer, and death. Safe and effective vaccines against HBV have been available in the United States (US) for decades. The success of universal childhood immunization against HBV, recommended by the Advisory Committee on Immunization Practices (ACIP), has led to a decline in acute HBV infection in the US. Currently, adults 30-49 YOA have the greatest incidence of acute and newly reported chronic HBV in the US; individuals in this age group did not receive universal immunization against HBV during childhood. Reduced seroprotection rates of HBV vaccines have been observed with increasing age, obesity, diabetes, male gender, smoking, and concomitant disease (Schillie, 2018; Averhoff, 1998).

In support of approval for use of Sci-B-Vac in individuals ≥18 YOA, the Applicant submitted the results of Sci-B-Vac-001 and Sci-B-Vac-002, two randomized, double-blind, active-controlled trials in adults, including 2,920 subjects who received at least one dose of Sci-B-Vac. Effectiveness of a three-dose series was evaluated based on non-inferiority to a US-licensed comparator 4 weeks after the third dose as measured by the seroprotective rate (SPR), the proportion of subjects achieving serum anti-HBs ≥10 mIU/mL, an established correlate of protection against HBV infection. In each of the trials, collection of safety data was similar and included solicited local (injection site pain, tenderness, pruritus, redness, and swelling) and systemic (nausea/vomiting, diarrhea, headache, fatigue, myalgia, and fever) adverse events recorded on a diary card by all subjects for 7 days following each dose, unsolicited adverse events (AEs) recorded on a diary card for 28 days following each dose, and serious adverse events (SAEs), medically attended adverse events (MAAEs), and new-onset chronic illnesses (NOCIs) from the first dose through 6 months following the third dose. Both studies assessed hematology and chemistry laboratory parameters following each dose in a subset of at least 10% of subjects.

Sci-B-Vac-001 was a Phase 3, multi-center, multi-national, double-blind, randomized, active-controlled trial to evaluate the immunogenicity and safety of Sci-B-Vac. A total of 1,607 HBV vaccine-naïve adults ≥18 YOA were enrolled and received at least one dose of a three-dose series of Sci-B-Vac or Engerix-B (active control) administered on Days 1, 28, and 168. To ensure adequate enrollment of older adults, subjects with controlled common chronic conditions were eligible and enrollment was targeted to 20% 18-44 YOA, 40% 45-64 YOA, and 40% ≥65 YOA. The study was designed to demonstrate non-inferiority of Sci-B-Vac compared to Engerix-B, as measured by SPR at Day 196, 4 weeks after the third dose, in all adults ≥18 YOA. The Applicant defined a second co-

primary objective to demonstrate the SPR following Sci-B-Vac was statistically higher than Engerix-B at Day 196 in adults ≥45 YOA. The first co-primary analysis was CBER's primary basis for licensure. Subjects were followed for safety and immunogenicity from first dose through Day 336, approximately 6 months following the third dose of vaccine.

The first co-primary endpoint of non-inferiority in adults ≥18 YOA was assessed on the Per Protocol Set (PPS), which consisted of subjects who were seronegative at baseline, had received all three doses, had evaluable serum immunogenicity samples at baseline and Day 196, and had no protocol deviations leading to exclusion (Sci-B-Vac group N=718, Engerix-B group N=723). In the PPS, the SPR was 91.4% (95% CI: 89.1, 93.3) in the Sci-B-Vac group and 76.5% (95% CI: 73.2, 79.5) in the Engerix-B group, resulting in a difference in SPR (Sci-B-Vac−Engerix-B) of 14.9%. The lower bound (LB) of the 95% CI of the difference in SPR was 11.2%, greater than the preset non-inferiority margin of −5%. Therefore, non-inferiority of Sci-B-Vac compared with Engerix-B 4 weeks after the third dose in subjects ≥18 YOA was demonstrated. The second co-primary endpoint was a comparison of SPRs assessed in adults ≥45 YOA seronegative at baseline in the Full Analysis Set (FAS), which consisted of subjects who received at least one dose and provided at least one evaluable serum immunogenicity sample at and after baseline (Sci-B-Vac group N=638, Engerix-B group N=646). In the FAS, SPR at Day 196 was 89.4% (95% CI: 86.8, 91.7) in the Sci-B-Vac group and 73.1% (95% CI: 69.4, 76.5) in the Engerix-B group, resulting in a difference in SPR (Sci-B-Vac−Engerix-B) of 16.4%. The LB of the 95% CI of the difference in SPR was 12.2%, which exceeded the Applicant's preset margin of >0%. The study met both of its co-primary endpoints.

Safety was evaluated in the Safety Set, consisting of subjects who received at least one dose of study product (Sci-B-Vac N=796, Engerix-B N=811). Injection site (IS) pain and tenderness were the most commonly reported solicited local symptoms after Sci-B-Vac administration, reported in a majority of subjects and at greater frequencies than in the Engerix-B group. Overall by subject, all doses considered, any grade (≥ Grade 3) pain at the IS was reported by 63.2% (0.1%) and 36.3% (0.1%) of subjects and IS tenderness was reported by 60.8% (1.0%) and 34.8% (0.4%) of subjects in the Sci-B-Vac and Engerix-B groups, respectively. Myalgia, headache, and fatigue were the most commonly reported solicited systemic symptoms after Sci-B-Vac administration. Overall by subject, all doses considered, any grade (≥ Grade 3) myalgia was reported by 34.7% (0.4%) and 24.3% (0.4%) of subjects, headache was reported by 31.3% (0.5%) and 29.3% (0.7%) of subjects, and fatigue was reported by 30.4% (0.7%) and 30.7% (1.6%) of subjects in the Sci-B-Vac and Engerix-B groups, respectively. Myalgia was the only solicited AE reported at a clinically significantly higher frequency in the Sci-B-Vac group compared to the Engerix-B group. Fever was uncommon, reported by 0.8% and 1.1% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. In general, local and systemic solicited symptoms tended to be reported at the highest frequencies in the Sci-B-Vac group following the first dose, with the exception of pruritus, which was reported at similar frequencies following each dose. Most local and systemic solicited AEs were reported at decreasing frequencies with increasing age.

There was a small numerical imbalance between treatment groups in the proportions of subjects in the Safety Set who reported SAEs during the study (32 subjects, 4.0% Sci-B-Vac and 21 subjects, 2.6% Engerix-B). One SAE of viral gastroenteritis occurring five days after dose two of Sci-B-Vac was assessed by the investigator as related and by the Applicant and CBER as not related to vaccination. No clinically significant between-group differences were noted with respect to the nature or timing of SAEs. There were

no clinically significant differences between treatment groups in the proportions of subjects in the Safety Set who reported unsolicited AEs (serious and non-serious) in the 28-day post-vaccination period and no differences noted in the nature of unsolicited AEs. No vaccine-related clinically significant safety laboratory abnormalities were identified.

Sci-B-Vac-002 was a Phase 3, multi-center, multi-national, double-blind, randomized, active-controlled trial to evaluate the manufacturing consistency, immunogenicity and safety of Sci-B-Vac. A total of 2,836 HBV vaccine-naïve adults 18-45 YOA were enrolled and received at least one dose of a three-dose series of one of three independent lots of Sci-B-Vac or with Engerix-B (active control) administered on Day 1, 28, and 168. The primary objective was evaluation of manufacturing equivalence between the three Sci-B-Vac lots as determined by adjusted geometric mean concentration (GMC) ratios of anti-HBs at Day 196, 4 weeks after the third dose. The secondary objective was demonstration of non-inferiority of Sci-B-Vac to Engerix-B at Day 196. Subjects were followed for safety and immunogenicity from first dose through Day 336, approximately 6 months following the third dose of vaccine.

The primary endpoint of lot-to-lot consistency was assessed on the PPS1, which consisted of all subjects who were seronegative at baseline, received all three doses, had evaluable serum immunogenicity samples at baseline and Day 196, and had no protocol deviations leading to exclusion (Sci-B-Vac Lot A N=620, Sci-B-Vac Lot B N=622, Sci-B-Vac Lot C N=627). In the PPS1, mean adjusted GMCs of anti-HBs at Day 196 were 5,882.25 mIU/mL, 4,821.65 mIU/mL, and 5,569.89 mIU/mL across Lots A, B, and C of Sci-B-Vac, respectively. The adjusted GMC ratios (95% CIs) among the three lot groups were Lot A vs. Lot B: 0.82 (0.67, 1.00), Lot A vs. Lot C: 0.95 (0.78, 1.15); and Lot B vs. Lot C: 1.16 (0.95, 1.41). Lot-to-lot consistency was demonstrated as the two-sided 95% CIs for the adjusted GMC ratios between lots were within the pre-specified margin of [0.67, 1.5]. The secondary endpoint of non-inferiority (in adults 18-45 YOA) was assessed on the PPS2, which consisted of subjects in the PPS1 excluding those whose visits at Day 168 or 196 occurred out of the defined window (pooled Sci-B-Vac group N=1,778, Engerix-B group N=603). In the PPS2, the SPR was 99.3% (95% CI: 98.7, 99.6) in the pooled Sci-B-Vac group and 94.8% (95% CI: 92.7, 96.4) in the Engerix-B group, resulting in a difference in SPR (pooled Sci-B-Vac−Engerix-B) of 4.5%. The LB of the 95% CI of the difference in SPR was 2.9%, greater than the preset non-inferiority margin of −5%. Therefore, non-inferiority of Sci-B-Vac compared with Engerix-B 4 weeks after the third dose (in subjects 18-45 YOA) was demonstrated.

In the Safety Set for Sci-B-Vac-002 (pooled Sci-B-Vac group N=2,124, Engerix-B group N=712) IS pain and tenderness were the most commonly reported solicited local symptoms after Sci-B-Vac administration, reported in a majority of subjects and at greater frequencies than in the Engerix-B group. Overall by subject, all doses considered, any grade (≥ Grade 3) IS pain was reported by 75.6% (0.9%) and 53.9% (0.4%) of subjects and IS tenderness was reported by 75.1% (2.1%) and 54.9% (0.7%) of subjects in the pooled Sci-B-Vac and Engerix-B groups, respectively. Myalgia, fatigue, and headache were the most commonly reported solicited systemic symptoms after Sci-B-Vac administration. Overall by subject, all doses considered, any grade (≥ Grade 3) myalgia was reported by 44.4% (1.2%) and 32.4% (1.0%) of subjects, fatigue was reported by 40.1% (1.6%) and 39.9% (1.5%) of subjects, and headache was reported by 38.2% (0.8%) and 37.6% (1.1%) of subjects in the pooled Sci-B-Vac and Engerix-B groups, respectively. Myalgia was the only solicited AE reported at a clinically significantly higher frequency in the Sci-B-Vac group than in the Engerix-B group. Fever

was uncommon, reported by 1.1% of subjects in both groups. In the Sci-B-Vac group, local and systemic solicited symptoms tended to be reported at the highest frequencies following the first dose, with the exception of IS pruritus and fever, which were reported at slightly higher rates following dose 3 compared to dose 1. No clinically significant differences in reactogenicity were identified between the three lots of Sci-B-Vac.

In the Safety Set, SAEs were reported more frequently in the Sci-B-Vac group (42 subjects, 2.0%) than in the Engerix-B group (3 subjects, 0.4%). SAEs generally consisted of conditions typically experienced by individuals of the age and health status of the study population, with infections and injuries being the most commonly reported classes of events. No SAEs were assessed as vaccine-related, and the nature or timing of the SAEs did not suggest a vaccine-related safety concern. The single reported death was a 35-year-old man who died of sudden cardiac death due to hypertrophic heart disease (b) (6) days after dose 1 of Sci-B-Vac. This death was assessed by the investigator as unrelated and CBER agrees with this assessment. There were no clinically significant differences between treatment groups in the proportions of subjects in the Safety Set who reported unsolicited AEs (serious and non-serious) in the 28-day post-vaccination period. Fatigue (reported in 3.8% Sci-B-Vac and 2.4% Engerix-B) and dizziness (reported in 1.5% Sci-B-Vac and 0.8% Engerix-B) were the most frequently reported unsolicited AEs that were also reported clinically significantly more frequently in the Sci-B-Vac group. No vaccine-related clinically significant safety laboratory abnormalities were identified.

Post-vaccination safety assessment methodology was similar across both pivotal studies, enabling integration across studies to identify patterns of AEs and assess for the occurrence of uncommon adverse events. The Safety Analysis Set of the integrated pivotal studies consisted of 2,920 subjects who received at least one dose of Sci-B-Vac and 1,523 subjects who received at least one dose of Engerix-B. The proportion of subjects who reported SAEs from Days 1-336 was higher in the Sci-B-Vac group compared to the Engerix-B group (74 subjects, 2.5% Sci-B-Vac and 24 subjects, 1.6% Engerix-B), while SAEs within 28 days of any dose were reported at relatively similar rates between groups (25, subjects, 0.9% Sci-B-Vac and 9 subjects, 0.6% Engerix-B). Four subjects in the Sci-B-Vac group reported SAEs of appendicitis with onset 4-110 days following any dose. These events were not clustered in time to suggest vaccine relationship. No patterns of SAE type or timing were observed to suggest a vaccine-related risk. In general, overall proportions of unsolicited AEs (serious and non-serious) were reported at similar rates in both vaccine groups. The Applicant identified the following unsolicited AEs following Sci-B-Vac, for which available information suggests a causal relationship to vaccination and which will be included in the package insert: injection site bruising (1.4%), dizziness/vertigo (1.1%), general pruritus/itchiness (0.2%), arthralgia (0.2%), urticaria/hives (0.2%) and lymphadenopathy/lymph node pain (0.1%).

In addition to data from the two pivotal studies described above, the Applicant provided synopses of non-IND studies evaluating the proposed formulation and dose regimen or non-IND studies evaluating prior formulations of Sci-B-Vac or different dose regimens. Review of these synopses did not alter the safety or effectiveness assessment of the proposed Sci-B-Vac dose and formulation.

As this BLA was an application for approval of a new active ingredient, the Pediatric Research Equity Act (PREA) was triggered. The Applicant requested and was granted a full waiver for studies in all pediatric age groups because this product does not represent

a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

In conclusion, the two pivotal clinical trials, enrolling 2,920 subjects receiving at least one dose of Sci-B-Vac, demonstrated non-inferiority of a three-dose regimen of Sci-B-Vac, administered by intramuscular (IM) injection at Days 1, 28, and 168, to a US-licensed HBV vaccine based on SPR (the proportion of subjects achieving anti-HBs ≥10 mIU/mL, the established correlate of protection for HBV infection). Manufacturing equivalence was also demonstrated, as well as immunogenicity across subgroups. Reactogenicity, particularly local, occurred in a majority of subjects. Severe reactogenicity was uncommon and reactions typically resolved in 1-2 days. These data demonstrate substantial evidence of effectiveness, as well as safety, and are supportive of licensure Sci-B-Vac to prevent infection by all known subtypes of HBV in adults ≥18 YOA. The Applicant's proposed pharmacovigilance plan, which includes a postmarketing commitment to establish a pregnancy registry, is adequate to assess safety in postmarketing use of the vaccine.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Efficacy analyses by age, gender, race and ethnicity

Immune responses to Sci-B-Vac were determined by the SPR, the proportion of subjects who achieved a post-vaccination serum hepatitis B surface antibody (anti-HBs) ≥10 mIU/mL, a level indicative of protection from hepatitis B virus (HBV) infection and disease. Immune responses by demographic subgroups were assessed 4 weeks after the third dose independently in the two studies, Sci-B-Vac-001 and Sci-B-Vac-002. The studies were not powered to evaluate differences in immune response for demographic subgroups, and the clinical significance of any differences noted in these analyses is unknown. Subjects vaccinated in Sci-B-Vac-001, had a median age of 58.0 years (range: 18-90) and majorities were female (61.5%), non-Hispanic or Latino (90.0%) and White (89.9%). Subjects vaccinated in Sci-B-Vac-002, had a median age of 35.0 years (range: 18-45) and majorities were female (57.8%), non-Hispanic or Latino (90.3%) and White (91.5%).

In study Sci-B-Vac-001, the two age groups of subjects younger than 65 YOA had higher immune response rates than the group of subjects ≥65 YOA. The seroprotective rates (SPR) (95% CI) were 99.2% (95.6, 100.0) in subjects 18-44 years of age (YOA), 94.8% (91.8, 96.9) in subjects 45-64 YOA, and 83.6% (78.6, 87.8) in subjects aged ≥65 YOA. An age-related decline in immune response to hepatitis B virus vaccines has been documented and a more pronounced decline of SPR with increasing age was seen in Sci-B-Vac-001 for the US-licensed comparator group.

There was a difference in immune response to Sci-B-Vac by gender, only apparent in Sci-B-Vac-001; the SPR (95% CI) in the Sci-B-Vac group was 94.3% (91.7, 96.3) for women and 86.9% (82.4, 90.6) for men. In Sci-B-Vac-002, the SPR differed between genders by less than 1%.

No clinically significant differences were observed in immune responses to Sci-B-Vac in either study by race or ethnicity.

Safety analyses by age, gender, race and ethnicity

Safety in demographic subgroups was assessed by combining results of two trials evaluating Sci-B-Vac compared to another US-licensed hepatitis B vaccine (Engerix-B). For the analysis of adverse events solicited via a diary card by age, only the results of Sci-B-Vac-001 are presented below. Subjects enrolled in the two studies were majority female (59.1%), not Hispanic/Latino (90.2%), and White (90.9%). Subjects in the Sci-B-Vac group were younger than those in the Engerix-B group (median age 38.0 years and 43.0 years, respectively). The studies were not powered to evaluate differences in safety based on demographic groupings and the clinical significance of any differences noted between groups in the below analyses is unknown. Because the proportions of subjects in some racial groups were too low to analyze separately, for the purposes of analyzing safety by race, the Applicant grouped subjects into the following (proportions of the vaccinated population are in parentheses): Black or African American (6.6%), Asian (1.3%), White (90.9%), and Other (1.2%, including American Indian or Alaska Native, Native Hawaiians or Pacific Islander, or Other).

Serious adverse events (SAEs): From study Days 1-336, in the combined population of the two studies, SAEs were reported more frequently in the Sci-B-Vac than the Engerix-B group (2.5% Sci-B-Vac; 1.6% Engerix-B), though no SAEs were assessed as related by the Applicant and CBER. By age, SAEs were reported more frequently in the Sci-B-Vac group in the youngest (18-44 YOA: 2.1% Sci-B-Vac; 0.4% Engerix-B) and oldest age groups (≥65 YOA: 4.7% Sci-B-Vac; 2.4% Engerix-B). Among subjects 45-64 YOA, SAEs were reported at similar frequencies between vaccine groups (3.5% Sci-B-Vac; 3.7% Engerix-B). The overall incidence of SAEs increased with increasing age in the Sci-B-Vac group (18-44 YOA: 2.1%, 45-64 YOA: 3.5%, ≥65 YOA: 4.7%), as would typically be expected. No clinically significant pattern in the type or timing of SAEs was observed that would indicate a specific risk following vaccination in any age group.

As in the overall combined study population, SAEs were reported more frequently in the Sci-B-Vac group compared to the Engerix-B group in women (2.7% Sci-B-Vac; 1.5% Engerix-B) and men (2.4% Sci-B-Vac; 1.7% Engerix-B). In White subjects, as in the study overall, subjects in the Sci-B-Vac group reported more SAEs than subjects in the Engerix-B group (2.6% Sci-B-Vac; 1.5% Engerix-B). In Black or African American subjects, SAEs were more frequent in the Engerix-B group (3 subjects, 1.6% Sci-B-Vac; 3 subjects, 2.9% Engerix-B), but were reported in few subjects overall. In non-Hispanic or Latino subjects, as in the study overall, subjects in the Sci-B-Vac group reported SAEs more frequently than subjects in the Engerix-B group (2.7% Sci-B-Vac; 1.5% Engerix-B). In Hispanic or Latino subjects, SAEs were reported at similar frequencies between groups (3 subjects, 1.1% Sci-B-Vac; 2 subjects, 1.3% Engerix-B), but were reported in few subjects overall. Differences in SAE incidence by demographic subgroups generally reflected the differences in the overall combined study population, particularly for the largest demographic subgroups. No differences likely to be clinically significant were observed by subgroup.

Unsolicited adverse events (serious and non-serious) reported during the 28-day post-vaccination periods: Following Sci-B-Vac, the proportion of subjects reporting unsolicited AEs decreased with increasing age group (18-44 YOA: 50.1%, 45-64 YOA: 45.8%, ≥65 YOA: 38.9%). In the Sci-B-Vac group, a higher proportion of females reported AEs than males (54.5% and 39.8%, respectively), but these rates were similar between vaccine groups by gender. In the Sci-B-Vac group, the proportions of subjects reporting unsolicited AEs during the 30-day post-vaccination period by race ranged from 31.1%

(Asian race) to 50.0% (Other race). By race, the proportions of subjects reporting unsolicited AEs were similar between vaccine groups, with the exception of Other race (50.0% Sci-B-Vac; 39.1% Engerix-B); this group had the smallest number of subjects and the difference may have occurred by chance. The proportion of non-Hispanic or Latino subjects (50.2%) reporting unsolicited AEs within 28 days of any dose of Sci-B-Vac was higher than that in the Hispanic or Latino group (31.4%), but between vaccine groups unsolicited AEs were reported at similar frequencies by ethnicity.

Common AEs solicited from subjects during the 7-day post-vaccination periods: Among Sci-B-Vac recipients in Sci-B-Vac-001, the incidence of solicited AEs decreased with increasing age for both local injection site (18-44 YOA: 80.7%, 45-64 YOA: 76.3%, ≥65 YOA: 62.2%) and systemic (18-44 YOA: 73.1%, 45-64 YOA: 59.7%, ≥65 YOA: 42.9%) symptoms. In Sci-B-Vac-001 and Sci-B-Vac-002 combined, the proportions of females in the Sci-B-Vac group reporting solicited local and systemic symptoms (86.5% and 70.8%, respectively) was higher than males (74.4% and 56.5%, respectively). By race, incidence of solicited local AEs ranged from 55.6% in Black or African American subjects to 83.3% in White subjects; incidence of solicited systemic AEs ranged from 42.3% in Black subjects to 71.1% in Asian subjects. Hispanic or Latino subjects were less likely to report local (60.6%) and systemic (50.0%) solicited AEs following Sci-B-Vac than non-Hispanic or Latino subjects (83.5% and 66.3%, respectively).

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	

☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

HBV is transmitted between persons via blood or sexual contact and causes an acute or chronic inflammation of the liver. Clinical manifestations of acute infection can range from asymptomatic infection to fulminant hepatitis. Symptomatic illness is observed in 30%-50% of older children, adolescents, and adults, although fulminant hepatitis is uncommon. Approximately 95% of primary infections in immunocompetent adults are self-limited. Chronic infection is more frequent in immunosuppressed persons, including individuals on hemodialysis, with HIV infection, and with diabetes. Chronic infection can cause cirrhosis, liver cancer, liver failure, and death. Premature death occurs in approximately 15% of those who become chronically infected after childhood (Schillie, 2018).

The World Health Organization estimates that in 2019, more than 296 million people worldwide were chronically infected with HBV, and an estimated 820,000 people died due to HBV. Approximately 1.5 million new infections occur each year. (World Health Organization, 2021). In the US, an estimated 1.25 to 2.49 million persons are living with chronic HBV (Lim, 2020). A total of 13,859 new chronic hepatitis B cases were reported to the CDC in 2019, 47% were in persons aged 30-49 years (CDC, 2021). Foreign-born persons account for approximately 95% of newly reported chronic infections in the US; the majority of chronic HBV infections in the US are among Asians/Pacific Islanders (Schillie, 2018).

In the US, since the start of universal childhood vaccination in 1991, the incidence of HBV infection has substantially decreased from 8.5 per 100,000 in 1990 to 1 per 100,000 in 2019. In 2019, the incidence of acute hepatitis B was highest for persons aged 40-49 years (2.7 cases/100,000) (CDC, 2021). The Advisory Committee on Immunization Practices (ACIP) also previously recommended HBV vaccination for all adults requesting protection from HBV infection and for all unvaccinated adults at risk of HBV infection (Schillie, 2018). Adults at risk of acquiring HBV include those at risk of sexual exposure (for example, sexual partners of hepatitis B surface antigen [HBsAg]-positive persons, persons with multiple partners in the previous 6 months, persons evaluated for a sexually transmitted disease), with current or recent use of injection drugs, with potential exposure via mucosal surfaces or blood (for example, household contacts of HBsAg-positive persons, healthcare and public safety personnel, individuals receiving dialysis, and individuals <60 YOA with diabetes mellitus), and with other risk factors (for example, international travelers to endemic countries, persons with chronic liver disease). ACIP recently updated its recommendation to universal vaccination of individuals 19 - 59 YOA and vaccination of those ≥60 YOA with risk factors for hepatitis B infection. Individuals ≥60 YOA without known risk factors may also receive hepatitis B vaccination (ACIP, 2021).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Vaccination against HBV is the primary means of preventing HBV infection. In addition to vaccination, non-pharmacologic interventions to prevent HBV infection in adults include "universal precautions" in healthcare settings, avoidance of sexual contact with infected individuals, condoms, avoidance of other high-risk behaviors (for example, injection drug use, tattoos, and body piercings), and use of sterile needles for those high-risk behaviors. If an acute hepatitis B exposure is known, post-exposure prophylaxis may include hepatitis B immune globulin and vaccination with a licensed hepatitis B vaccine.

Antiviral medications are available for the treatment of certain subjects with chronic HBV infection. Management of chronic HBV is complex, requires lengthy, sometimes toxic regimens, and depends on multiple factors, including clinical, immunologic, and virologic factors. Antiviral medications recommended for use in adults with chronic HBV include pegylated interferon and nucleoside and nucleotide reverse transcriptase inhibitors, such as entecavir and tenofovir (Terrault, 2018).

2.3 Safety and Efficacy of Pharmacologically Related Products

Four licensed vaccines are available in the US for the prevention of HBV infection in adults. Two licensed vaccines, Engerix-B (GSK, 2019) and Recombivax HB (Merck, 2018), FDA-licensed in 1989 and 1986, respectively, contain a single antigen and are adjuvanted with aluminum. Both are made from yeast-derived recombinant antigen adsorbed to aluminum compounds. Engerix-B (20 mcg, 1.0 mL) and Recombivax HB (10 mcg, 1.0 mL) are both licensed as a three-dose series in adults, administered at 0, 1, and 6 months. One combination vaccine is available for adults, Twinrix (GSK, 2019) FDA-licensed in 2001, which includes an inactivated hepatitis A virus component, a yeast-derived recombinant hepatitis B component (20 mcg), and aluminum adjuvants. Twinrix is licensed as a three-dose series (1.0 mL), administered at months 0, 1, and 6. Additionally an accelerated schedule is licensed for Twinrix as a series of four doses, given on Days 0, 7 and Days 21 to 30, followed by a booster dose at Month 12. The fourth vaccine available to adults, Heplisav-B (Dynavax, 2019), FDA-licensed in 2017, contains a yeast-derived-recombinant HBV antigen (20 mcg) and a cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide phosphorothioate adjuvant. Heplisav-B is licensed as a two-dose series (0.5 mL each) on a 0- and 1-month schedule.

In immunocompetent individuals, vaccine-induced serum hepatitis B surface antibody (anti-HBs) ≥10 mIU/mL is recognized as seroprotective against HBV infection (Jack, 1999). All of the US-licensed HBV vaccines are highly effective based on pivotal clinical trials demonstrating a seroprotective antibody response in >90% of healthy adults (GSK, 2019; Merck, 2018; GSK, 2019; Dynavax, 2019). Long-term studies of immunocompetent adults and children indicate that for individuals who respond to HBV vaccines, immune memory remains intact for up to three decades and suggest protection against symptomatic acute and chronic HBV infection, even though anti-HBs antibody concentrations may become low or undetectable over time (Bruce, 2016; Simons, 2016; Zanetti, 2005). In practice, medical and behavioral characteristics have been identified that contribute to decreased seroprotective responses to HBV vaccination, including smoking, obesity, aging, chronic medical conditions, drug use, diabetes, male sex, genetic factors, and immune suppression (Schillie, 2018, Averhoff, 1998).

The three aluminum-adjuvanted vaccines (Engerix-B, Recombivax HB, and Twinrix) have 20 years or more of use in the US and extensive data to support their safety. All four of the above vaccines are contraindicated in individuals with previous severe allergic reactions to HBV vaccines or vaccine components, including yeast. Although several neurologic, chronic, and immunologic diseases have been reported in temporal association with HBV vaccines, evidence of a causal relationship is not established (Stratton, 2012; Schillie, 2018). With regard to the CpG-adjuvanted vaccine (Heplisav-B), licensed in 2017, a postmarketing requirement study to assess the risk of acute myocardial infarction following vaccination and a postmarketing commitment study to assess risk of immune-mediated diseases, herpes zoster, and anaphylaxis are currently outstanding; however, no safety signals have been identified through postmarketing surveillance.

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

Sci-B-Vac first received marketing authorization in Israel in 2000, under the tradename Bio-Hep-B. It was subsequently approved in other countries in Asia, Africa, and South America, and marketed in Israel and Hong Kong. Three formulations were marketed for use in neonates, children, and adults: 2.5 mcg and 5 mcg of HBsAg in 0.5 mL for use in neonates, infants, and children depending on the country and HBV endemicity, and 10 mcg of HBsAg in 1.0 mL for adolescents and adults. It is administered as a three-dose regimen at months 0, 1 and 6. Sci-B-Vac is currently marketed in Israel and is available on a "named-patient basis" in several European countries.

Reviewer comment: *The Applicant sought licensure for use in individuals ≥18 YOA only. Please see section 5.4.2 for additional details. A "named-patient basis" allows physicians to obtain medicines directly from manufacturers prior to authorization. Authorization is also being sought through European Medicines Agency.*

Sci-B-Vac is formulated with aluminum hydroxide ($Al(OH)_3$; 0.5 mg/mL) as an adjuvant. Previous pre-market formulations used during clinical development contained thimerosal (b) (4) mcg/mL) as a preservative, which was removed in 1998, and aluminum phosphate ($AlPO_4$; (b) (4) mg/mL) as an adjuvant, which was changed to $Al(OH)_3$ in 1994.

Reviewer comment: *Some non-IND studies, synopses of which were submitted in support of this BLA, used previous formulations of Sci-B-Vac (see section 9.2).*

Sci-B-Vac was not marketed from 2005 through 2008, during the technical transfer of the product from Biotechnology General to SciGen (forerunner to VBI Vaccines Inc.). During the cumulative period from the international birth date (February 9, 2000) to the data lock point (June 14, 2020), the estimated number of vials of Sci-V-Bac sold is (b) (4) . Assuming that all individuals completed the recommended three-dose regimen, the cumulative exposure to the product is estimated to be approximately (b) (4) individuals, including approximately (b) (4) adults.

Since the international birth date in 2000 until the present, the Applicant reports that no serious related adverse reactions attributable to the vaccine, as determined by the manufacturer, have been identified in the spontaneous reporting system nor in the clinical studies conducted. In response to an information request (IR), the Applicant submitted a five-year analysis of postmarketing data for the time period April 2016 to April 2021 (125737/0.6). The results of this analysis consisted of three reports of

adverse drug reactions in three adults reporting eight non-serious events after vaccination with Sci-B-Vac that were reported to pharmacovigilance (PV) during the specified time period. The manufacturer assessed one event as related. The reported events were:

- Throat pain, Pharyngitis, Lymphadenopathy (neck), Fever, and Glossopharyngeal neuralgia in a 49-year-old man, resolved after 18 days
- Foot and palm pain in a 22-year-old woman, resolved after 3.5 weeks
- Alanine transaminase (ALT) elevated (144 IU/L) and HBs antigenemia in a 69-year-old man on hemodialysis, with heart disease, diabetes and metabolic syndrome, resolved after 20 days. The HBs antigenemia was assessed by the manufacturer as related.

In response to an IR (125737/0.24), the Applicant attributed the low number of postmarketing safety reports to the mostly young healthy population administered vaccine in Israel, the favorable safety profile, a limited distribution of the vaccine in the market, and lack of a marketing strategy to encourage safety reporting. In addition to review of spontaneous reports, the Applicant conducts literature searches and reviews the results of investigator-initiated studies evaluating Sci-B-Vac. The Applicant notes that several investigator-initiated clinical studies evaluated the immunogenicity and safety of Sci-B-Vac in patients with high-risk underlying medical conditions such as HIV infection, celiac disease, and end-stage kidney disease, with no concerning safety signals identified (data not submitted to CBER).

Reviewer comment: *To date, postmarketing safety monitoring is not robust. See section 4.6 for a description of the pharmacovigilance plan (PVP).*

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

The following list references key milestones in the clinical development program for Sci-B-Vac, related primarily to IND 17542 and the current BLA; amendment numbers below refer to amendments submitted to that IND.

Sep-10-2012	Master File (b) (4) was initially opened and included chemistry, manufacturing, and controls (CMC), nonclinical, and clinical information. At the time, the Applicant stated their intent to support the clinical development for use in individuals with (b) (4) . CBER provided advice via an IR in January 2013 and a pre-IND meeting in May 2013. In November of 2013, CBER asked for additional information to be submitted to the Master File.
Dec-21-2016	Master File (b) (4) was updated to include, among other information clinical study reports for four non-IND studies to inform the discussion at the anticipated pre-IND meeting.
Apr-10-2017	A Pre-IND meeting was held to discuss the Applicant's plans for initiation of two pivotal Phase 3 studies to support US licensure in all adults. At the time CBER advised on study design, safety follow-up, and against inclusion of any claims of superiority in the package insert (meeting minutes dated May 5, 2017).
Jul-26-2017	Initial IND submission (Amendment 0) containing protocols for two IND, Phase 3 clinical trials, Sci-B-Vac-001 and Sci-B-Vac-002.

Sep-27-2017	A consultation with the Pediatric Review Committee (PeRC) regarding the initial pediatric study plan (iPSP) was held. Please see section 5.4.2 for details.
Oct-03-2019	Type C Meeting to discuss the proposed content of the safety database. CBER agreed that a database consisting of approximately 2,923 subjects would be sufficient for assessment of safety, assuming no safety signals were identified. At the time, CBER advised the Applicant to include summaries of four supportive trials at the time of the BLA submission and advised the Applicant to address events of Grade 4 solicited local AEs (meeting minutes dated Oct 10, 2019).
Oct-2018 through Jul-2020	Multiple submissions (Amendments 32, 34, 36, 38, 39, 40, 41, 45, 47, 48, 56), CBER communications (Oct 25, 2018, Nov 20, 2018, Feb 7, 2019, Feb 15, 2019, Mar 26, 2019, Apr 18, 2019, Jun 26, 2019, Aug 27, 2019, Feb 12, 2020, May 8, 2020, June 9, 2020), and a teleconference between CBER and the Applicant (May 21, 2020) regarding the Applicant's Study Data Standardization Plan, case report forms, and the structure of the Applicant's datasets
May-13-2020	A Type B Pre-BLA meeting was held to discuss the Applicant's proposal for BLA submission (Amendment 52). At this time CBER advised the Applicant on requirements for the integrated summary of safety (ISS), including a request to include summaries of all adult studies of Sci-B-Vac (and previous formulations) for a more comprehensive assessment of safety (meeting minutes dated June 12, 2020).
Jan-29-2021	Date to reach a determination on filing status. No major issues were identified that the Applicant was unable to address by this date and the application was determined to be fileable. CBER determined that a Vaccines and Related Biological Products Advisory Committee meeting was not required.
Oct-12-2021	The PeRC reviewed the Applicant's request for the full waiver and the Division's agreement. Please see section 5.4.2 for details.

2.6 Other Relevant Background Information

Not Applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

During the course of the review, specific issues were identified with safety data collection and reconciliation processes. For example, subjects were able to assess solicited adverse events as Grade 4, and the Applicant declined to include investigator revisions to the grading of solicited AEs in the solicited AE datasets, as previously advised by CBER. This led to several solicited AEs, most notably local solicited AEs, assessed as Grade 4, for which the Applicant had no evidence in support of this grade (no evidence of medical attention, emergency room [ER] visit, or sequelae).

Reviewer comment: *Although the safety data collection process appears to have led to mis-categorization in the severity grading of some solicited AEs, these errors generally resulted in an over-assessment of risk of Sci-B-Vac. Please see additional details in sections 6.1.12 and 6.2.12.*

A number of errors were identified by the clinical reviewer within the datasets, clinical study reports (CSRs), and narratives, which included the following:

- Occasional incorrect coding of verbatim terms to Preferred Terms (PTs) and inconsistent coding between the two pivotal trials
- Occasional inconsistent information between the narratives and the datasets
- Occasional errors assumed to be data entry errors, which were not resolved at the time of data cleaning (for example, subject and site entry of erroneous grade 4 solicited AEs, resolved solicited AEs listed as new-onset chronic illnesses)
- Erroneous presentation of the safety laboratory data in the Sci-B-Vac-002 CSR and appended tables
- Inconsistencies within the safety laboratory dataset, including missing laboratory normal ranges for a subset of subjects and one site in Sci-B-Vac-001 that assessed blood urea instead of blood urea nitrogen (BUN), for which the Applicant did not correctly apply a conversion, resulting in an unexpectedly high number of Grade 3 laboratory abnormalities that were reported in the CSR and not clarified or corrected by the Applicant.

When narratives and datasets were in conflict, the reviewer used information in the datasets, unless the narrative included a clarification specific to the inconsistency. The Applicant was queried regarding incorrect or inconsistent coding and other errors that had the potential to affect the reviewer's safety assessment. Inconsistent coding between studies affected few events overall. Therefore, the results presented here reflect the safety data as originally coded in the datasets and presented in the CSRs and ISS. The reviewer's unsolicited AE analyses considered groups of AEs when appropriate (for example, Standardized MedDRA Queries [SMQs], Medical Dictionary for Regulatory Activities [MedDRA] hierarchy), minimizing the impact of the incidents of inconsistent coding. Please see section 5.2 for a listing of BLA submissions, including those addressing clinical IRs.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The two pivotal trials, Sci-B-Vac-001 and Sci-B-Vac-002, were conducted under IND and in accordance with current Good Clinical Practice (GCP) and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. The Applicant states that these trials were approved by an Institutional Review Board, Independent Ethics Committee, or Research Ethics Board at each study site before the study began. Written informed consent was obtained from subjects as per GCP requirements. During the conduct of all of the submitted studies, the Applicant identified no significant deviations from GCP compliance.

Some of the non-pivotal trials, whose study synopses were submitted as supportive to the current BLA, were conducted before the initial registration of Sci-B-Vac in 2000 or were conducted or initiated prior to the adoption of the ICH Guideline on GCP (E6 (R1)) by the FDA. The Applicant states these trials were conducted under standards that were in place at the time that each study was conducted, including the Declaration of Helsinki.

3.3 Financial Disclosures

The Applicant certified that they did not enter into any financial arrangement with any clinical investigators of the two pivotal studies whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), that each clinical investigator was required to disclose whether the investigator had a proprietary interest in Sci-B-Vac or a significant equity in the Applicant as defined in 21 CFR 54.2(b) and none disclosed any such interests, and that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Reviewer comment: *Initially, the Applicant included only principal investigators (125737/0.1) but provided financial information on sub-investigators in a later amendment (125737/0.29). The Applicant did not identify any reportable financial arrangements with any investigators. Thus, there was no indication that financial arrangements would impact the overall integrity of the data submitted.*

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Sci-B-Vac is formulated with aluminum hydroxide as an adjuvant, along with excipients of sodium chloride (NaCl), potassium chloride (KCl), disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4 \cdot 12H_2O$), potassium dihydrogen phosphate anhydrous (KH_2PO_4) and water for injection. The HBsAg is purified from the supernatant of Chinese hamster ovary (CHO) cells by a series of physicochemical steps. Each dose may contain residual amounts of CHO cell proteins, CHO cell DNA, bovine serum albumin, and formaldehyde.

Reviewer comment: *At the time of finalizing this review, no major issues had been identified by Chemistry, Manufacturing, and Controls (CMC). Please see the CMC review for details.*

4.2 Assay Validation

Evaluations of the effectiveness of Sci-B-Vac was based on post-vaccination immune response measured by VITROS anti-HBs quantitative chemiluminescence assay, which was independently validated for use within the central laboratory performing the immunogenicity assessments.

Reviewer comment: *At the time of finalizing this review, no major issues had been identified. Please see the CMC and Statistical reviews for further details.*

4.3 Nonclinical Pharmacology/Toxicology

Of several nonclinical toxicology studies performed during the development of Sci-B-Vac, the two studies described below are pertinent to this BLA as they evaluated the current formulation of Sci-B-Vac.

Repeat-dose toxicity study: A non-good laboratory practices (GLP) repeat-dose toxicity study (the testing facility was not GLP certified at the time the study was performed in 2004) in (b) (4) rats evaluated (b) (4) of Sci-B-Vac at dose levels of 2 mcg and 10 mcg HBsAg with $Al(OH)_3$ compared to $Al(OH)_3$ adjuvant alone administered by intramuscular (IM) injection at 2-week intervals (Day 0, 14, 28). Animals were sacrificed at 2 days after

the last dose or at 8 weeks following recovery. There were no unexpected clinical signs or treatment-related changes in body weights or organ weights following Sci-B-Vac treatment. Leukocytosis was observed in some animals at comparable incidence in all groups, suggesting relationship with the aluminum adjuvant. Histopathological changes were restricted to discrete lymphoid hyperplasia, occurring more in vaccine than in adjuvant groups, and adjuvant deposition with mononuclear cell infiltrate at the injection sites of some animals.

Developmental and reproductive toxicity study: This study in (b) (4) rats evaluated 1.0 mL of 10 mcg HBsAg and (b) (4) mcg $Al(OH)_3$ administered IM at two sites (0.5 mL each) compared to placebo and placebo with aluminum adjuvant on Day 30 and Day 15 prior to mating and on gestation days 4 and 15. No adverse effects of pre-weaning development were observed. There were no female reproductive effects and no effects on fetal/embryonal development and postnatal development up to Day 23.

Reviewer comment: *Nonclinical evaluation did not identify any unexpected vaccine-related findings. Please see the toxicology review for additional details.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Sci-B-Vac is a recombinant, alum-adjuvanted hepatitis B vaccine, produced by expression of the Pre-S1 (large), Pre-S2 (middle) and S (small) protein components of HBV surface antigen (HBsAg) in CHO cells. According to the Applicant, Sci-B-Vac resembles the naturally occurring HBV particles in terms of protein composition, glycosylation pattern and harbors all antigenic epitopes and domains of the HBV envelope.

Post-vaccination antibody concentrations ≥10 mIU/mL to HBsAg are recognized as conferring protection against HBV infection (Jack, 1999).

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Based on the results obtained in the initial dose-ranging studies, conducted during 1989 to 1993, the 10 mcg dose level was selected for further development in adults, given 1) the higher rates of seroprotection observed at earlier timepoints than the 5 mcg formulation, 2) the higher peak anti-HBs levels achieved one month after the third dose, at Month 7, and 3) comparable tolerability and safety profiles.

4.5 Statistical

The statistical reviewer verified that the submitted data supported the primary and pertinent secondary immunogenicity results of the pivotal clinical trials, including lot consistency and non-inferiority immunogenicity analyses.

Reviewer comment: *Please refer to the statistical review for details.*

4.6 Pharmacovigilance

Please see section 2.4 regarding previous postmarketing safety monitoring. For the PVP, the Applicant identified no important risks or potential risks with the use of Sci-B-Vac and identified only missing information as a safety concern. The PVP includes routine risk minimization and routine pharmacovigilance activities to address the missing information regarding concomitant use with other vaccines, seroconversion in patients with immunological function impairment, and use in pregnancy and lactation. In addition, the Applicant proposes a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Sci-B-Vac during pregnancy. The Applicant also notes that they have contracted with a third-party to perform pharmacovigilance (PV) services.

Reviewer comment: *The PV reviewer agrees with routine pharmacovigilance, as proposed by the Applicant in the PVP, with adverse event reporting as required under 21 CFR 600.80. CBER requested that the pregnancy registry be a postmarketing commitment.*

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Review focused on the safety and immunogenicity evaluations of Sci-B-Vac in adults, based upon the results of the two pivotal IND studies submitted in the BLA. The basis for licensure was primarily viewed as the non-inferiority comparisons between Sci-B-Vac and the licensed comparator in all adults ≥18 YOA. Non-IND study synopses were reviewed to determine if any additional safety concerns were identified. CBER did not request that the Applicant submit data from the non-IND studies because 1) the safety database and immunogenicity evaluations of the pivotal trials were anticipated to be sufficient, 2) the non-IND studies evaluated current and prior formulations of Sci-B-Vac, and 3) the safety monitoring and follow-up did not necessarily meet the standards routinely requested by CBER.

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

The sBLA documents that served as the basis for the clinical review are presented below. Cover letters for each amendment were also reviewed. For the IND documents that served as a reference, please see section 2.5.

Nov-30-2020	125737/0.0	Modules 1.2 (Cover Letter, Reviewer's Guide, and Clinical Site Summary List), 1.3 (Administrative information, including Debarment Certification and Financial Disclosure), 1.6 (Meetings), 1.9 (Pediatric Administrative information), 1.14 (Labeling), 1.16 (Risk Management Plan), 1.18 (Proprietary Name), 2.2 (Introduction), 2.5 (Clinical Overview), 2.7 (Clinical Summary), 5.2 (Tabular Listing of all Clinical Studies), 5.3.4 (Reports of Human Pharmacodynamic Studies), 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication), 5.3.5.2 (Study Reports of Uncontrolled Clinical Studies), 5.3.5.3 (Reports of Analyses of Data from More than One Study)

Jan-26-2021	125737/0.1	Module 1.3.4 (Administrative information, Financial Certification and Disclosure) – List of Investigators
Apr-22-2021	125737/0.5	Modules 1.11.3 (Clinical Information Amendment), 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication), 5.3.5.3 (Reports of Analyses of Data from More than One Study) – Datasets clarifications related to CDISC validation
Apr-30-2021	125737/0.6	Module 1.11.3 (Clinical Information Amendment) – Postmarketing data
May-07-2021	125737/0.7	Modules 1.11.4 (Multiple Module Information Amendment), 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) – information pertaining to responses to April 23, 2021 comments 1 through 3 regarding immunogenicity values above the upper limit of quantitation and integrated safety dataset
Jun-08-2021	125737/0.10	Modules 1.11.3 (Clinical Information Amendment), 1.16.1 (Risk Management) – Pregnancy registry synopsis
Jul-30-2021	125737/0.19	Modules 1.11.3 (Clinical Information Amendment), 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication), 5.4 (Literature References) – Clinical events including a summary of and narratives for pregnancies, grade 4 solicited local AEs, potential allergic reactions, and other specific AEs, datasets clarifications and advice, Sci-B-Vac-001 Addendum with cell-mediated immunity and pre-S1 and Pre-S2 immune responses
Aug-19-2021	125737/0.20	Module 1.11.3 (Clinical Information Amendment) – Pregnancy registry milestone dates
Sep-01-2021	125737/0.22	Module 5.3.5.1 (Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) – Updated Sci-B-Vac-002 signature page
Sep-07-2021	125737/0.24	Module 1.11.3 (Clinical Information Amendment) – Postmarketing data
Sep-27-2021	125737/0.25	Module 1.11.3 (Clinical Information Amendment) – Information on protocol deviations, specific AEs
Oct-05-2021	125737/0.27	Module 1.11.3 (Clinical Information Amendment) – Revised calculations for Grade 3 AEs excluding SAEs, medically attended adverse events (MAAEs) through 28 days following vaccination, and solicited systemic events with fever included
Oct-19-2021	125737/0.29	Module 1.3.4 (Administrative information, Financial Certification and Disclosure) – List of Investigators, including sub-investigators
Oct-26-2021	125737/0.31	Module 1.11.3 (Clinical Information Amendment) – specific AEs, clinical laboratory safety data clarifications, and events in the supportive studies.
Nov-05-2021	125737/0.34	Modules 1.11.3 (Clinical Information Amendment) and 1.14 (Labeling) – Revised package insert
Nov-09-2021	125737/0.35	Modules 1.11.3 Clinical Information Amendment and 1.16.1 Risk Management – Pregnancy registry milestone dates and revised synopsis

Nov-10-2021	125737/0.36	Modules 1.11.3 (Clinical Information Amendment) and 1.14 (Labeling) – Revised package insert
Nov-15-2021	125737/0.37	Module 1.11.3 (Clinical Information Amendment) – multi-site investigators and clinical laboratory safety data clarifications.
Nov-23-2021	125737/0.40	Modules 1.11.3 (Clinical Information Amendment) and 1.14 (Labeling) – Revised package insert, carton and container labels
Nov-29-2021	125737/0.42	Modules 1.11.3 (Clinical Information Amendment) and 1.14 (Labeling) – Revised package insert
Nov-29-2021	125737/0.43	Modules 1.11.3 (Clinical Information Amendment) and 1.14 (Labeling) – Revised package insert

Labeling negotiations were ongoing at the time the clinical review was finalized.

Reviewer comment: *IRs from CBER were adequately addressed by the Applicant.*

5.3 Table of Studies/Clinical Trials

Table 1. Pivotal, Phase 3 IND Trials[a] Pertinent to the Proposed Indication

Study Name (Year of Completion)	Objectives	Products[b] and Regimen	Number of Subjects (Safety Set)	Population	Duration
Sci-B-Vac-001 (2019)	Safety, immuno-genicity	2 arms: 1) Sci-B-Vac 10 mcg 2) Engerix-B 20 mcg IM on Days 1, 28, 168	N=1607 Sci-B-Vac: 796 Engerix-B: 811	Adults ≥18 YOA, including those with well-controlled chronic conditions	48 weeks
Sci-B-Vac-002 (2019)	Lot-to-lot consistency, safety, immuno-genicity	4 arms: Sci-B-Vac 10 mcg 1) Lot A 2) Lot B 3) Lot C 4) Engerix-B, 20 mcg IM on Days 1, 28, 168	N=2836 Sci-B-Vac: 1) 711 2) 708 3) 705 Engerix-B: 712	Healthy adults 18-45 YOA	48 weeks

Source: Adapted from 125737/0.0, Module 5.2, Tabular Listing of All Clinical Studies.
IM = intramuscular; N = total number of subjects vaccinated or in the specified vaccine group; YOA = years of age
a Both trials are randomized, double-blind, active-controlled, and conducted in the US, Canada and Europe
b Sci-B-Vac refers to the current formulation of Sci-B-Vac with $Al(OH)_3$ without thimerosal.

Table 2. Non-IND Trials Pertinent to the Proposed Indication

Study Identifier (Year of Completion)	Objectives	Design (Countries)	Products and Regimen[a]	Number of Subjects Vaccinated	Population	Duration
HBA9006S (1993)	Safety, immunogenicity	Phase 2, randomized, active-control, three-arm, open-label, single-center (Singapore)	Sci-B-Vac ($AlPO_4$ + thimerosal), 10 mcg Engerix-B, 20 mcg Hepavac II 10 mcg Months 0, 1, 6	N=300 100 Sci-B-Vac 100 Engerix-B 100 Hepavac II	Healthy adults 18-45 YOA	Follow-up to 1 year
38-92-001 (1994)	Safety, immunogenicity,	Phase 2, randomized, active-control, three-arm, single-blind, single-center (Israel)	Sci-B-Vac ($AlPO_4$ + thimerosal), 5 mcg Batch A, Batch B Engerix-B, 20 mcg Months 0, 1, 6	N=304 135 Batch A 118 Batch B 51 Engerix-B	Healthy adults 18-45 YOA	Follow-up to 1 year
38-96-040 (1998)	Safety, Immunogenicity	Phase 3, randomized, active-control, single-blind, 2-center (Israel)	Sci-B-Vac ($Al(OH)_3$ + thimerosal), 10 mcg Engerix-B, 20 mcg Months 0, 1, 6	N=524 260 Sci-B-Vac 264 Engerix-B	Healthy adults 18-60 YOA	Follow-up to 1 year
HBV-002 (2003)	Safety, Immunogenicity	Phase 3, randomized, active-control, open-label, multi-center (Switzerland, Netherlands, Austria, Israel)	Sci-B-Vac ($Al(OH)_3$ without thimerosal) (b) (4) mcg Engerix-B, 20 mcg single dose with dose 2 given on Day 85 if anti-HBs <100 mIU/mL	N=716 479 Sci-B-Vac 237 Engerix-B	Adults ≥18 YOA, low and non-responders to prior HBV vaccine (≥ four doses)	Follow-up to Day 120, approxi-mately 1 month post-dose 2 (if given)
SG-005-05 (2008)	Safety, Immunogenicity	Phase 3, randomized, active-control, single-blind, three-arm, single-center (Vietnam)	Sci-B-Vac ($Al(OH)_3$ without thimerosal), 10 mcg Batch A Batch B Engerix-B, 20 mcg Days 0, 30, 180	N=402 134 Batch A 134 Batch B 134 Engerix-B	Healthy adults 18-45 YOA	Follow-up to 1 year

Study Identifier (Year of Completion)	Objectives	Design (Countries)	Products and Regimen[a]	Number of Subjects Vaccinated	Population	Duration
38-13-040 (2015)	Safety, Immunogenicity	Phase 3, randomized, active-control, double-blind 3-center (Russia)	Sci-B-Vac ($Al(OH)_3$ without thimerosal), 10 mcg Engerix-B, 20 mcg Days 0, 28, 180	N=100 50 Sci-B-Vac 50 Engerix-B	Healthy adults 18-45 YOA	Follow-up to 7 months, 1 month post-dose 3
HB-88002 S (1990)	Safety, Immunogenicity	Phase 2, dose-ranging, open-label, single-center (Singapore)	Sci-B-Vac ($AlPO_4$ + thimerosal), 5 mcg 10 mcg Months 0, 1, 6	N=99 49 (5 mcg) 50 (10 mcg)	Healthy adults 18-45 YOA	Follow-up to 1 year
HB-88002 T (1991)	Safety, Immunogenicity	Phase 2, dose-ranging, open-label, single-center (Thailand)	Sci-B-Vac ($AlPO_4$ + thimerosal), 5 mcg 10 mcg Months 0, 1, 6	N=53 26 (5 mcg) 27 (10 mcg)	Healthy adults 18-45 YOA	Follow-up to 1 year
HBV-003-89 (1993)	Safety, Immunogenicity	Phase 2, dose-ranging, open-label, single-center (Israel)	Sci-B-Vac ($AlPO_4$ + thimerosal), 5 mcg 10 mcg Months 0, 1, 6	N=147 43 (5 mcg) 104 (10 mcg)	Healthy adults 18-45 YOA	Follow-up to 1 year
38-92-001 (Extension) (1995)	Safety, Immunogenicity	Phase 2, single-arm, extension, open-label, single-center (Israel)	Sci-B-Vac ($Al(OH)_3$ + thimerosal), 5 mcg Months 0, 1, 6	N=85	Healthy adults 18-45 YOA	Follow-up to 1 year
SciB018 (2017)	Safety, Immunogenicity	Phase 4, single-arm open-label, single-center (Israel)	Sci-B-Vac ($Al(OH)_3$ without thimerosal), 10 mcg Months 0, 1, 6	N=91	Healthy adults 20-40 YOA	Follow-up to 1 year

Source: Adapted from 125737/0.0, Module 5.2, Tabular Listing of All Clinical Studies.
$Al(OH)_3$ = Aluminum hydroxide; $AlPO_4$ = Aluminum phosphate; IM = intramuscular; N = number of subjects vaccinated or in the specified vaccine group; YOA = years of age
a All doses were administered intramuscularly.

5.4 Consultations

5.4.1 Advisory Committee Meeting

CBER determined that an Advisory Committee meeting was not needed because FDA review of information submitted in the BLA, including the clinical study design and trial

results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

5.4.2 External Consults/Collaborations

The Applicant requested a full waiver of studies in all pediatric age groups. The statutory rationale for the full waiver [see section 505B(a)(4)(A)(iii) of the Food, Drug and Cosmetic Act] was that this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. On September 27, 2017, a consultation with the PeRC regarding the iPSP was held. The PeRC did not agree with the Applicant's plan for no pediatric assessment of Sci-B-Vac in the US, noting that this vaccine could potentially be used in a substantial number of neonates in the US based on ACIP recommendations. The Division agreed with the Applicant that Sci-B-Vac does not represent a meaningful benefit over existing therapy for pediatric patients and is not likely to be used in a substantial number of pediatric patients. On October 12, 2021, the PeRC reviewed the request for the full waiver and the Division's reasoning for granting it. A majority of PeRC members agreed to a full pediatric waiver for all pediatric subgroups, with a few members disagreeing.

Reviewer's comment: *There are four highly effective and safe hepatitis B vaccines available for use in subsets of children and adolescents, including two combination vaccines that are preferentially used in infants. The Division did not think that a substantial number of children would use this vaccine given available alternatives with extensive US use and an established safety profile.*

5.5 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

Sci-B-Vac-001: 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 SPR 4 weeks after completion of the three-dose regimen of Sci-B-Vac is non-inferior to the SPR 4 weeks after completion of the three-dose regimen of Engerix-B in adults ≥18 YOA
- To demonstrate that the SPR 4 weeks after completion of the three-dose regimen of Sci-B-Vac is superior to the SPR 4 weeks after completion of the three-dose regimen of Engerix-B in older adults ≥45 YOA

Reviewer comment: *At the time of the initial IND submission, CBER advised the Applicant that CBER considered the non-inferiority analysis for the entire study*

population to be the primary analysis that would support licensure, and that all other analyses were considered supportive. CBER also advised that while results of analyses may be considered for presentation in labeling, claims of superiority would not as statistical superiority does not establish clinical superiority.

Secondary objectives

- To determine whether the SPR after receiving two doses of Sci-B-Vac, evaluated at 4 weeks and 20 weeks after receiving the second dose (just prior to receiving the third vaccination), is non-inferior to the SPR 4 weeks after receiving the third dose of Engerix-B
- To compare the safety and reactogenicity of Sci-B-Vac and Engerix-B

Select exploratory objectives

- To compare the geometric mean concentration (GMC) of anti-HBs, 4 weeks after receiving the first dose, the second dose and the third dose, 20 weeks after receiving the second dose (just prior to receiving the third dose), and 24 weeks after receiving the third dose of Sci-B-Vac or Engerix-B
- To compare the SPR observed 4 weeks after receiving the first dose and second dose, 20 weeks after receiving the second dose (just prior to receiving the third vaccination), and 24 weeks after receiving the third dose of Sci-B-Vac or Engerix-B at Study Days 28, 56, 168 and 336
- To compare SPR and GMC in subgroups of interest (for example, body mass index [BMI] >30 kg/m^2), 4 weeks after receiving the third dose of Sci- B-Vac or Engerix-B
- To assess the antibody responses against pre-S1 and pre-S2 at baseline, 4 weeks after each dose of Sci-B-Vac or Engerix-B and at Study Days 168 and 336
- To compare the boost, relative to baseline, of cell-mediated immune response against HBsAg, 1 week after each dose of either Sci-B-Vac or Engerix-B (optional sub study at select sites)

Reviewer comment: *A number of additional exploratory objectives were defined, including the proportion of subjects with anti-HBs ≥100 mIU/mL post-vaccination. The clinical benefit of anti-HBs ≥100 mIU/mL in this population is not established; only the exploratory objectives potentially contributing to the risk-benefit assessment are discussed below.*

6.1.2 Design Overview

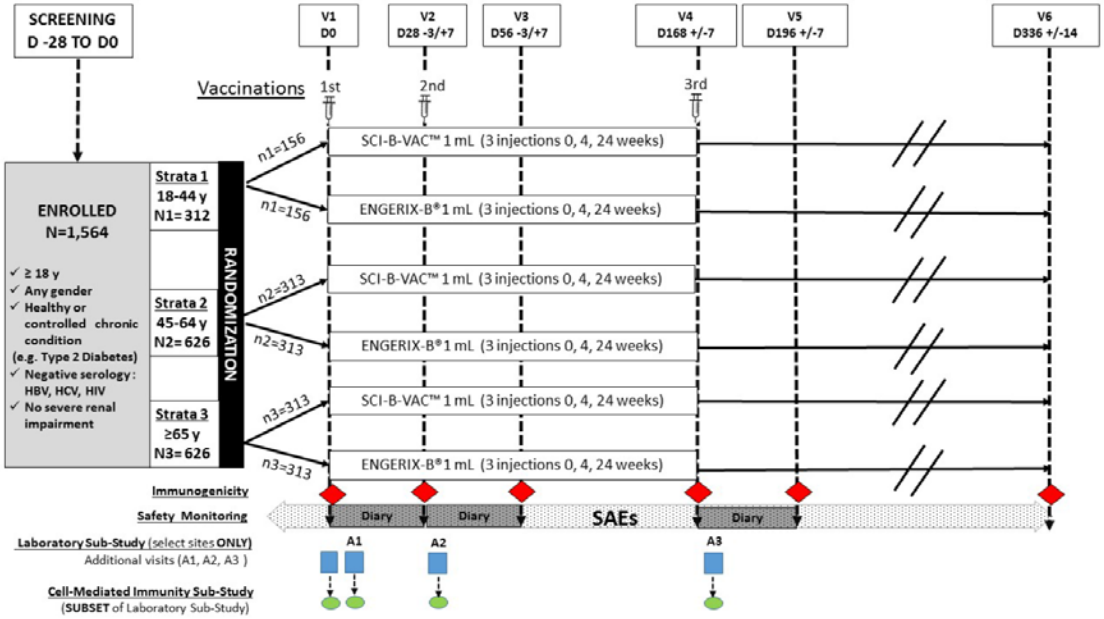
This study was a double-blind, randomized, active-controlled trial to assess non-inferiority of Sci-B-Vac compared to Engerix-B in adults ≥18 YOA. Subjects were randomized 1:1 to receive a three-dose series of either Sci-B-Vac or Engerix-B, administered IM on Day 0, 28, and 168. Randomization was stratified by study center and age (18-44 YOA, 45-64 YOA, and ≥65 YOA). Enrollment to the ≥45 years age groups was targeted to 80% of study population (40% for each group) to ensure adequate power to evaluate the second co-primary objective (superiority of Sci-B-Vac in adults ≥45 YOA) and to ensure good representation across the spectrum of older adults.

The study included a 4-week screening period to determine subject eligibility. Enrolled subjects visited the study sites for a total of 7 visits (screening and V1 through V6) and were followed for 48 weeks after the first dose, 24 weeks after receiving the third dose. There was a safety follow-up 7 days after each dose conducted by telephone to inquire

about local and systemic reactions. Based on these follow-up assessments, subjects may have been asked to come for a supplemental visit for clinical assessment if warranted. Safety evaluations included additional visits (A1 through A3) to perform laboratory testing (blood chemistry and complete blood count [CBC]) on Days 0 (V1), 7, 35, and 175 in a subset of subjects (at least 10% of the total number of subjects) enrolled at select study sites. Immunogenicity (measurement of anti-HBs, pre S1 and pre S2 antibodies) was assessed at baseline and on Days 28, 56, 168, 196, and 336. A schematic of the study design is provided below.

Reviewer comment: *Cell-mediated immunity, Pre S1 and pre S2 antibody results were not submitted as part of the initial BLA submission but were submitted in a later amendment (125737/0.19). They are not discussed further in this review as these are exploratory objectives that are not expected to impact the regulatory decision.*

Figure 1. Study Design, Sci-B-Vac-001



Source: 125737/0.0, Sci-B-Vac-001 Protocol, p. 22.
D = Study day; V = Visit; N = Number of subjects; n = number of subjects in the subset; y = years of age

6.1.3 Population

Key inclusion criteria

- Individuals 18 YOA and older
- Able and willing to provide consent
- In stable health as determined by a physical examination and laboratory tests. Common chronic conditions such as, but not limited to, type 2 diabetes, high blood pressure, chronic obstructive pulmonary disease, and asthma were allowed if the condition was well-controlled, as determined by the investigator, and not meeting the exclusion criteria. For subjects >65 years old, Frailty Index ≤3
- If a woman of childbearing potential, agreed to use an acceptable method of contraception during the screening period and through the end of study participation

Key exclusion criteria

- Previous vaccination with any HBV vaccine
- Current or past hepatitis B infection (anti-HBc, anti-HBs, HBsAg performed at screening)
- Known hepatitis C infection unless treated and cured; Known HIV
- Renal impairment with glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 at screening
- Uncontrolled diabetes mellitus (hemoglobin A1C [HbA1C] >8.5%)
- Uncontrolled hypertension (average systolic blood pressure [SBP] ≥150 mmHg or average diastolic blood pressure [DBP] ≥95 mmHg based on the last three measurements
- Any laboratory test abnormality ≥ Grade 1 severity and clinically significant as per the investigator, or ≥ Grade 3 severity, regardless of investigator's clinical assessment.
- Advanced stage heart failure
- History of cancer requiring chemotherapy or radiation within 5 years
- History of allergic or anaphylactic reaction to any vaccine component of either vaccine
- Treatment with immunosuppressant within 30 days
- Known history of immunological function impairment, including autoimmune disease, primary or secondary immunodeficiency
- Pregnant or breastfeeding
- Live attenuated vaccine within 4 weeks or inactivated vaccine within 2 weeks prior to enrollment
- Receipt of blood products or immunoglobulin within 90 days or granulocyte-macrophage colony stimulating factor or erythropoietin within 30 days of enrollment, or likely to receive during the study

Reviewer comment: *Subjects with common chronic conditions were eligible for enrollment to ensure adequate enrollment of older adults.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study products were:

- Sci-B-Vac: supplied as 1 mL single-dose vials. Each vial contained 10 mcg of hepatitis B surface antigens (pre-S1, pre-S2, and S) adsorbed on 0.5 mg aluminum hydroxide. The product also contained sodium chloride, potassium chloride, disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate anhydrous and water for injection. Lot number: B1291V1.
- Engerix-B: supplied as 1 mL single-dose vials. Each vial contained 20 mcg of HBsAg-S adsorbed on 0.5 mg aluminum hydroxide. Lot number: B39CM.

6.1.5 Directions for Use

Either Sci-B-Vac or Engerix-B was administered to subjects as a three-dose series in a volume of 1 mL by IM injection in the deltoid on Days 0, 28, 168. The first dose was given in the deltoid muscle of the nondominant arm and subsequent doses were alternated between the dominant and nondominant arms.

6.1.6 Sites and Centers

The study was conducted at 28 study centers including 7 in Canada, 1 in Belgium, 10 in Finland, and 10 in the US.

Table 3. Number of Subjects by Center, Country, and Region, Sci-B-Vac-001, Safety Set

Country	Site Number	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Canada	**All sites**	**126 (15.8)**	**133 (16.4)**
Canada	100	31 (3.9)	33 (4.1)
Canada	101	4 (0.5)	3 (0.4)
Canada	103	45 (5.7)	47 (5.8)
Canada	104	14 (1.8)	14 (1.7)
Canada	105	15 (1.9)	16 (2.0)
Canada	114	0 (0.0)	3 (0.4)
Canada	115	17 (2.1)	17 (2.1)
United States	**All sites**	**338 (42.5)**	**342 (42.2)**
United States	200	39 (4.9)	38 (4.7)
United States	202	44 (5.5)	45 (5.5)
United States	203	35 (4.4)	37 (4.6)
United States	204	36 (4.5)	36 (4.4)
United States	205	40 (5.0)	37 (4.6)
United States	206	34 (4.3)	35 (4.3)
United States	207	44 (5.5)	44 (5.4)
United States	208	23 (2.9)	20 (2.5)
United States	209	28 (3.5)	31 (3.8)
United States	210	15 (1.9)	19 (2.3)
Europe	**All sites**	**332 (41.7)**	**336 (41.4)**
Belgium	300	32 (4.0)	31 (3.8)
Finland	601	31 (3.9)	31 (3.8)
Finland	602	32 (4.0)	32 (3.9)
Finland	603	32 (4.0)	32 (3.9)
Finland	604	36 (4.5)	35 (4.3)
Finland	605	30 (3.8)	32 (3.9)
Finland	606	25 (3.1)	27 (3.3)
Finland	607	31 (3.9)	33 (4.1)
Finland	608	29 (3.6)	27 (3.3)
Finland	609	21 (2.6)	22 (2.7)
Finland	610	33 (4.1)	34 (4.2)

Source: 125373/0.0 Sci-B-Vac-001 CSR, Table 16, pp. 66-68; and 125737/0.25 Table 1, pp. 3-4.
Note: Site is the initial site of subject randomization.
N = number of subjects in the total group; n (%) = number and percent of subjects enrolled at the clinical site.

Reviewer comment: *Study sites in the US enrolled the most subjects of the three regions, with 42.3% of the total study population, followed closely by Europe, consisting mostly of sites in Finland. Enrollment across sites was well distributed with no site enrolling more than 6% of the total study population.*

6.1.7 Surveillance/Monitoring

Study oversight
Study center monitoring, including monitoring by designated unblinded personnel, was Conducted by (b) (4)

An independent Data Monitoring Committee (DMC), comprising five members, was established to monitor subject safety. Members of the DMC were responsible for reviewing safety reports and data and, in the event a stopping rule was triggered, determining whether the clinical trial was to be stopped or required modification to proceed safely.

Safety assessments – solicited AEs
Solicited AEs were assessed in the 30-minute post-vaccination period.

Subjects were issued diary cards to record solicited symptoms daily beginning the day of vaccination and continuing for 6 days following each dose, including the maximum symptom intensity or measurement and the end date. The following local symptoms were solicited: redness/erythema, pain, swelling/edema, tenderness, and pruritus. The solicited systemic AEs for this study were nausea/vomiting, diarrhea, headache, fatigue, and myalgia.

Reviewer comment: *Subjects also monitored temperature daily during the solicited AE assessment period. The Applicant called temperature an "other" solicited AE (see below). As fever is typically collected as a solicited systemic AE and was collected on the diary card with the local and systemic solicited AEs, CBER analyzed fever as a solicited systemic AE.*

Solicited AEs were graded according to the FDA Guidance for Industry (FDA, 2007). The diary card contained the following questions for subjects under redness and swelling:

- Redness: Was there any exfoliative dermatitis (peeling over large areas of the skin) or skin necrosis (death of skin cells)?
- Swelling: Was there any skin necrosis (death of skin cells)?

When the subject answered yes to either of these questions, the grade was recorded as 4. The protocol specified that staff would review the diary card entries with subjects.

Reviewer comment: *The diary card was reviewed and deemed acceptable for its intended purpose. Prior to the BLA submission (IND 17542, CBER communications dated February 12, 2020 and March 11, 2020), CBER advised the Applicant how to record the investigator's assessment in the datasets, if it differed from the subject's diary card entry. The Applicant opted to include only subject assessment of solicited AEs in the solicited AE datasets. When investigator assessment was recorded, it was reported in the unsolicited AE dataset. This process led to several Grade 4 solicited AEs, primarily injection site (IS) redness and swelling, being reported (see section 6.1.12.2).*

Oral temperature, blood pressure (systolic/diastolic), heart rate, and respiratory rate were assessed at baseline and at each vaccination visit, before and 30 minutes following vaccination. The Applicant defined these as "other" solicited AEs. If a subject had a fever (defined as temperature ≥38.0°C/100.4°F oral) on the day of and prior to vaccination, the vaccination visit was rescheduled within the allowed interval for the visit. Any abnormal vital sign after vaccination was reassessed. Subjects were also given an oral thermometer for recording daily body temperature on the day of vaccination and for the next 6 days (Days 1 through 7 post-vaccination as for solicited AEs). Toxicity grading of vital signs was by FDA Guidance for Industry (FDA, 2007). The following was the grading scale for fever:

- Grade 1 (Mild): 38.0–38.4°C, 100.4–101.1°F

- Grade 2 (Moderate): 38.5–38.9°C, 101.2–102.0°F
- Grade 3 (Severe): 39.0–40°C, 102.1–104°F
- Grade 4 (Potentially life-threatening): >40°C, >104°F

Safety assessments – unsolicited AEs (SAEs, MAAEs, and NOCIs)
AEs and SAEs were defined as per 21 CFR 312.32.

Unsolicited AEs were collected using the diary card beginning the day of vaccination and continuing for the next 27 days. The diary card had space to record the intensity of the AE, the start and end dates, whether medical attention was sought for the AE, and whether medication was taken. At study visits diary cards were reviewed and unsolicited AEs were recorded in the electronic case report form (eCRF). The investigator determined the causal relationship of unsolicited AEs (very likely/certain, probable, possible, unlikely, unrelated, unclassifiable). Events assessed as having a very likely/certain, probable, or possible relationship to vaccination are considered "related" in the analyses below, unless otherwise specified. The outcomes of any unsolicited AE occurring within 30 days of vaccination and each SAE were recorded. Unsolicited AEs were graded according to the following scale:

- Grade 1 (Mild): No interference with daily activity
- Grade 2 (Moderate): Some interference with daily activity but not requiring medical intervention
- Grade 3 (Severe): Prevents daily activity and requires medical intervention
- Grade 4 (Potentially life-threatening): Requiring ER visit or hospitalization

Reviewer comment: *Although the above grading scale was specified, investigators were able to use their judgement in grading severity and thus, not all ER visits led to a Grade 4 severity grade. While it is possible that some investigators graded differently than others depending on whether they were strictly following the protocol or following the Applicant's advice, differential grading between treatment groups would not be expected due to observer-blinding. The Applicant classified AEs without a severity grade specified by the investigator as Grade 4, potentially life-threatening. While safety data is not typically imputed, there were few AEs without a severity grade, and the imputed severity likely resulted in a higher severity grade for some events.*

Solicited AEs continuing beyond Day 7 and solicited AEs meeting the definition of an SAE were also considered unsolicited AEs and captured in the unsolicited AE dataset.

For each symptom subjects reported, the subject was asked if it was medically attended, defined as hospitalization, ER visit, or an otherwise unscheduled visit to or from medical personnel for any reason, including ER visits. Medically attended solicited AEs were not considered unsolicited AEs unless they fit the above criteria (clarification provided in 125737/0.19).

SAEs, medically attended AEs (MAAEs), medically significant events, and new-onset chronic illnesses (NOCIs) were reported from the first dose to the End of Study Visit 6 months after the third dose (V6, Day 336). In the protocol, medically significant AEs were defined as a condition prompting an ER visit, physician visit not related to a common disease/not a routine visit, or an SAE not related to a common disease. MAAEs were not defined in the protocol.

Reviewer comment: *In 125737.025, the Applicant clarified that collection of medically attended events was via a query on the CRF asking if the event was medically attended and what type of medical attention (ER visit, doctor's office, hospitalization, unscheduled study visit). Therefore, although medically significant events were specified in the protocol, including as safety endpoints, due to the difficulty with operationally defining medically significant events, the Applicant collected MAAEs instead. The manner in which the Applicant actually collected this data is consistent with typical safety data collection.*

The Applicant collected AEs considered NOCIs, for which a specific definition was not included in the protocol. The Applicant noted a diverse range of AEs reported as NOCIs during the conduct of the study, and subsequently provided an assessment of NOCIs conducted by the contract research organization's medical monitor (MM) using the Centers for Disease Control and Prevention (CDC) listing of chronic diseases (NCCDPHP 2019) as a reference.

Reviewer comment: *This review will summarize NOCIs identified by the investigators or MMs in order to capture the greatest number of NOCIs.*

Safety phone call

A safety phone call was conducted seven (+/- 2) days after each vaccination to inquire about local and systemic reactogenicity. A scripted set of questions asked about severe (Grade 3) solicited AEs. Subjects were also reminded to complete the diary cards and return them at their next study visit.

Reviewer comment: *Scripted questions asked subjects about severe redness and swelling based on measurement only and did not specifically ask about exfoliative dermatitis, peeling, skin necrosis, or cell death (recorded on the diary cards). Although the safety phone call did ask about other changes in health, local AEs identified as Grade 4 based on subject assessment of those symptoms, were not identified during the safety phone call for further assessment.*

Stopping rules

Individual stopping rules included, among other criteria, a Grade 4 post-injection reaction within 7 days after any study injection, a clinically significant systemic reaction (in other words, angioedema, generalized urticaria) within 7 days after any study injection, Grade 3 or 4 hypotension within 24 hours after any study injection, and any life-threatening event within 7 days after any study injection, regardless of relationship.

Reviewer comment: *During the conduct of the study, solicited AEs assessed by subjects as Grade 4 (primarily redness and swelling) generally did not lead to treatment discontinuation, potentially because the investigator was not in agreement with the Grade 4 classification, or because they were not aware the subject had completed the diary card as such.*

Safety assessments – laboratory assessments and pregnancy

Eligibility screening assessments consisted of hematology, biochemistry, urinalysis, and serology (HBV, hepatitis C virus, and HIV) for all subjects and HbA1c for subjects with diabetes. At select sites, subjects were asked to participate in a clinical laboratory sub-study to include at least 10% of the total number of subjects enrolled in the trial. Subjects enrolled at these sites attended three additional visits (A1, A2, A3) and provided four

additional blood samples to assess hematology and biochemistry parameters pre-vaccination (V1), and 7 days following each vaccination. A subset of subjects participating in the laboratory sub-study participated in an optional sub-study on cell-mediated immunity.

Laboratory tests abnormalities were graded according to the Food and Drug Administration (FDA) Guidance for Industry (FDA, 2007). Safety laboratory evaluations were repeated if indicated (e.g., follow-up of a clinically significant laboratory abnormality from baseline assessment). Laboratory abnormalities were reported as AEs if they were accompanied by clinical symptoms, required a change in concomitant therapy, were present at baseline and significantly worsening following the start of the study, or were clinically significant by investigator judgement.

Urine pregnancy tests were performed at screening and prior to each vaccination. Pregnancies were recorded from the first dose through 4 weeks following the last dose and followed for outcome.

Reviewer comment: *Often pregnancy outcomes are monitored for all pregnancies that occur during a study, although the risk of vaccine-related events decreases the further from vaccination a pregnancy occurs. Please see section 9.1.1 for a summary of pregnancies and outcomes. A pregnancy registry is planned as a postmarketing commitment.*

Safety assessments – concomitant medications
Concomitant medications and vaccinations were collected at each study visit through the end of study (Day 336) and there was space on the diary card for recording them.

Immunogenicity assessments
A validated VITROS anti-HBs quantitative assay measured anti-HBs levels in serum at baseline, and at Study Days 28, 56, 168, 196, and 336.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint

- SPR at Study Day 196, 4 weeks after receiving the third dose of either Sci-B-Vac or Engerix-B.

  Seroprotection was defined as anti-HBs levels of ≥10 mIU/mL in serum and SPR was the percentage of subjects achieving seroprotection.

  Success criterion for each co-primary objective:
  - In adults ≥18 YOA, the lower bound of the two-sided 95% confidence interval (CI) of the difference between the SPR in the Sci-B-Vac arm minus the SPR in the Engerix-B arm, achieved 4 weeks after receiving the third dose, was >−5%
  - In adults ≥45 YOA, the lower bound of the two-sided 95% CI of the difference between the SPR in the Sci-B-Vac arm minus the SPR in the Engerix-B arm, achieved 4 weeks after receiving the third dose, is >5%

Reviewer comment: *Anti-HBs ≥10 mIU/mL is a generally accepted correlate of protection against HBV infection.*

Secondary endpoints

- (Immunogenicity) SPR at Study Days 56 and 168, 4 weeks and 20 weeks after receiving the second dose of Sci-B-Vac (just prior to receiving the third dose), and the SPR at Study Day 196, 4 weeks after receiving the third dose of Engerix-B
- (Safety) Number (%) of subject-reported, solicited AEs (on the day of vaccination and during the next 6 days), unsolicited AE (on the day of vaccination and during the next 27 days), and number of SAEs, medically significant events or NOCIs through Day 336
- (Safety) Number (%) of subjects with abnormal vital signs, and/or physical examination findings compared to baseline

Reviewer comment: *As noted above, MAAEs were collected and evaluated instead of medically significant events.*

Selected exploratory endpoints

- GMC of anti-HBs in serum, in both study arms, at baseline and at Study Days 28, 56, and 196, 4 weeks after each dose of either Sci-B-Vac or Engerix-B, and at Study Days 168 and 336
- SPR in both study arms at baseline and at Study Days 28, 56 and 168 and at Study Day 336
- Number (%) of subjects with abnormal clinical laboratory parameters from baseline assessments at Study Days 7, 35 and 175, one week after each dose of either Sci-B-Vac or Engerix-B (clinical laboratory sub-study, select sites)

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size

The sample size was selected based on the second co-primary analysis in subjects aged ≥45 years old and assuming an SPR of 81% for Engerix-B, SPR of 96% for Sci-B-Vac and targeted enrollment of 80% of subjects ≥45 YOA. The Applicant calculated a total enrollment of 680 adults (≥18 YOA) would provide ≥90% power to demonstrate non-inferiority with a 5% margin if the Sci-B-Vac SPR was as low as 88%, with SPR of 81% for Engerix-B, and a two-sided alpha of 0.05. The sample size was then increased to 1,564 subjects to guard against a higher SPR for Engerix-B.

Missing and implausible data

For immunogenicity data, missing values were considered as missing completely at random; imputation of missing data was not performed.

Local and systemic solicited AEs measured by the subjects were not subject to reconciliation. The following measurements were deemed implausible and are not included in the analyses: Body temperature ≤33°C (91.4°F) or ≥42°C (107.6°F); erythema ≥900 mm; and induration ≥500 mm.

Reviewer comment: *The Applicant imputed missing values for unsolicited AE severity as Grade 4 (potentially life-threatening) and missing values for relationship as very likely/certain). The Applicant did not impute severity for implausible measurements for solicited AEs. Imputations occurred rarely and reflect the most conservative safety assessment; they, as well as implausible measurements, are noted in the safety analyses presented below when clinically pertinent.*

Analysis of efficacy/immunogenicity
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 the (b) (4) titers.

The two co-primary analyses were tested sequentially.

The first co-primary immunogenicity analysis of non-inferiority of Sci-B-Vac in adults ≥18 YOA was based on the Per Protocol Set (PPS); sensitivity analyses were conducted using the Full Analysis Set (FAS). The second co-primary immunogenicity analysis of superiority of Sci-B-Vac in adults ≥45 YOA was based on the FAS excluding subjects seropositive at baseline; sensitivity analyses were conducted on the Intent-to-Treat population (ITT) and were reported both with and without subjects in the FAS or ITT who were seropositive at baseline. See section 6.1.10.1 for analysis population definitions.

Reviewer comment: *The FAS analysis of the second co-primary endpoint allowed a larger analysis population to assess differences in SPR in older subjects.*

First co-primary analysis – Non-inferiority in adults ≥18 YOA:
Null Hypothesis: SPR (Sci-B-Vac)-SPR (Engerix-B) ≤−5%
Alternative Hypothesis: SPR (Sci-B-Vac)-SPR (Engerix-B) >−5%
If the lower bound of the two-sided 95% CI was >−5%, Sci-B-Vac was declared non-inferior to Engerix-B.

Second co-primary analysis – Superiority adults ≥45 YOA:
Null Hypothesis: SPR (Sci-B-Vac)-SPR (Engerix-B) ≤5%
Alternative Hypothesis: SPR (Sci-B-Vac)-SPR (Engerix-B) >5%
If the lower bound of the two-sided 95% CI around the difference was >0%, the Applicant declared Sci-B-Vac statistically superior to Engerix-B. If the LB was >5%, the Applicant declared Sci-B-Vac clinically superior to Engerix-B.

Reviewer comment: *The Applicant proposes that a 5% margin represents a clinically meaningful improvement at the individual level and from a public health perspective, given reduced immunogenicity of licensed hepatitis B vaccines in the older adult population. It is CBER's position that demonstration of statistical superiority of SPR does not establish clinical superiority. Although humoral immunogenicity of anti-HBs is correlated with protection, it is not the only immune response induced by vaccination that contributes to protection.*

The estimated difference in SPRs and two-sided 95% CIs were calculated using the Miettinen and Nurminen method. Analyses of the co-primary endpoints were also conducted and reported for key subgroups based on demographic and clinical characteristics.

Secondary analyses: If the co-primary endpoints met the success criteria, the following secondary hypotheses were tested in the pre-specified below order, in a similar manner as the co-primary analyses above. If an endpoint failed to reach statistical significance, the next hypothesis test was not performed.

1. Non-inferiority of Sci-B-Vac 20 weeks following the second dose (Day 168) compared to Engerix-B 4 weeks following the third dose (Day 196) assessed using the PPS for the entire study population (adults ≥18 YOA) and a non-inferiority margin of 5%.
2. Non-inferiority of Sci-B-Vac 4 weeks following the second dose (Day 56) compared to Engerix-B 4 weeks following the third dose (Day 196) assessed using the PPS for the entire study population (adults ≥18 YOA) and a non-inferiority margin of 5%.

Reviewer comment: *As the first secondary analysis did not meet success criteria, the second analysis was not performed (see section 6.1.2).*

Exploratory analyses: Analyses of all exploratory immunogenicity endpoints were based on the PPS, unless otherwise indicated. Exploratory immunogenicity endpoints were summarized and analyzed without adjustment for multiple comparisons. GMCs were calculated based on observed immunogenicity concentrations and all statistical analyses were performed on the logarithmically transformed values. Adjusted estimates of GMCs and their associated 95% CIs at Days 28, 56, 168, 196, and 336 were each determined using an analysis of covariance (ANCOVA) model with factors for treatment, age group, and a covariate for the log-transformed pre-dose (baseline) titer. Imputation methods for missing data were not used.

Analysis of safety

The Safety Set (defined as all subjects who received at least one dose of vaccine, analyzed as treated) was the population used for most safety analyses. Clinical safety laboratory assessments were based on the Clinical Laboratory Sub-Study Analysis Set (SSA1). Safety analyses were descriptive and were provided by time of occurrence relative to the most recent dose as pre-specified in the study objectives. For unsolicited AEs, the verbatim terms reported by investigators in the eCRFs were mapped to PTs using MedDRA version 20.1.

Reviewer comment: *Please see the statistical review for further details about the statistical methods used for the immunogenicity and safety analyses.*

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The following analysis populations were defined:

- All Enrolled Set: All screened subjects who provided informed consent and demographic and/or baseline screening assessments.
- Safety Set: All subjects in the All Enrolled Set who received at least one dose of vaccine. Subjects were analyzed as treated.
- Intent-to-Treat (ITT) Set: All subjects in the All Enrolled Set who were randomized. Subjects in the ITT were analyzed as randomized. Any subject who received the wrong vaccine was not excluded from the ITT.
- Full Analysis Set (FAS): All subjects in the All Enrolled Set who received at least one dose of vaccine and provided at least one evaluable serum immunogenicity sample both at baseline and after baseline. Subjects were analyzed as randomized. If a subject was unblinded during the study, he/she was included in

the FAS. Any subject who received the wrong vaccine was not excluded from the FAS.

- Per Protocol Set (PPS): All subjects in the FAS who received all three doses, had evaluable serum immunogenicity samples at baseline and at the time point of interest, were seronegative at baseline, and had no major protocol deviations leading to exclusion as identified prior to unblinding. Subjects were analyzed as randomized and subjects who received the wrong vaccine were excluded. If a subject received a vaccine from the wrong kit number, but the same vaccine as the one the subject was randomized to, the subject was not excluded. If a subject was unblinded during the study, except due to a SUSAR, he or she could be excluded from the PPS based on Applicant's decision with respect to any potential bias that may be introduced.
- Clinical Laboratory Sub-Study Analysis Set (SSA1): All subjects in the All Enrolled Set who received at least one dose and participated in the clinical laboratory sub-study.

6.1.10.1.1 Demographics

The summary of demographic characteristics of the Safety Set is below. Majorities of subjects were female (61.5%), non-Hispanic or Latino (90.0%) and White (89.9%). As intended in the study design, subjects were well distributed by age group.

Table 4. Demographic Characteristics, Sci-B-Vac-001, Safety Set

Characteristic	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)	Total N=1607 n (%)
Gender			
Male	315 (39.6)	303 (37.4)	618 (38.5)
Female	481 (60.4)	508 (62.6)	989 (61.5)
Race			
White	715 (89.8)	730 (90.0)	1445 (89.9)
Asian	8 (1.0)	4 (0.5)	12 (0.7)
Black or African American	66 (8.3)	65 (8.0)	131 (8.2)
American Indian or Alaska Native	5 (0.6)	4 (0.5)	9 (0.6)
Native Hawaiian or other Pacific Islander	1 (0.1)	0	1 (0.1)
Other	1 (0.1)	8 (1.0)	9 (0.6)
Ethnicity			
Hispanic or Latino	79 (9.9)	75 (9.2)	154 (9.6)
Non-Hispanic or Latino	714 (89.7)	732 (90.3)	1446 (90.0)
Not collected per local guidelines	3 (0.4)	4 (0.5)	7 (0.4)
Age group (years)			
18-44	145 (18.2)	154 (19.0)	299 (18.6)
45-64	355 (44.6)	361 (44.5)	716 (44.6)
≥65	296 (37.2)	296 (36.5)	592 (36.8)
Age category (years)			
18-39	84 (10.6)	88 (10.9)	172 (10.7)
40-49	175 (22.0)	159 (19.6)	334 (20.8)
50-59	170 (21.4)	181 (22.3)	351 (21.8)
60-69	238 (29.9)	255 (31.4)	493 (30.7)
≥70	129 (16.2)	128 (15.8)	257 (16.0)
Age at informed consent (years)			
Mean (SD)	56.6 (13.2)	56.6 (13.5)	56.6 (13.3)
Median	57.0	58.0	58.0
Min, Max	18, 86	18, 90	18, 90

Characteristic	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)	Total N=1607 n (%)
Geographic location			
United States	338 (42.5)	342 (42.2)	680 (42.3)
Europe	332 (41.7)	336 (41.4)	668 (41.6)
Canada	126 (15.8)	133 (16.4)	259 (16.1)

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 16, pp. 66-68.
N = number of subjects in the total group; n (%) = number and percent of subjects with the demographic characteristic; max = maximum; min = minimum; SD = standard deviation

Reviewer comment: *There were no clinically significant between-group differences in demographics in the Safety Set. Very few Asians [0.7% overall, twice as many in the Sci-B-Vac group (1%) as the Engerix-B group (0.5%)] were enrolled in the study; Asian is a population of particular interest in evaluation of HBV vaccines (FDA, 2012). Black or African Americans and Hispanic or Latino subjects are also underrepresented compared to the US population.*

The Applicant presented demographics by vaccine group in the other analysis populations. No clinically significant between-group differences were noted in the FAS or PPS. In the Clinical Laboratory Sub-Study Analysis Set (SSA Set), no subjects were from the United States, 67.4% were from Canada, and 37.6% were from Europe. A lower percentage of subjects in this subset were Black or African American (2.1%) and Hispanic or Latino (5.7%) compared to the Safety Set (8.2% and 9.6%, respectively), though clinically significant between-group differences in race or ethnicity were not observed in this population. There were small between-group differences in the SSA1 population with regard to age category 18-39 years (10.4% of the Sci-B-Vac group and 5.2% of the Engerix-B group) and 50-59 years (25.0% of the Sci-B-Vac group and 30.9% of the Engerix-B group), which did not appear to affect clinically significant safety laboratory abnormalities.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The summary of medical and behavioral characteristics of the Safety Set is below. Most subjects were not obese (63.3%), non-smokers (59.9%), reported 0-1 alcoholic drink per day (91.9%), and were non-diabetic (92.2%). Subjects median BMI was 28.0 kg/m^2.

Table 5. Medical and Behavioral Characteristics, Sci-B-Vac-001, Safety Set

Characteristic	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)	Total N=1607 n (%)
BMI at Baseline (kg/m^2)			
Mean (SD)	29.42 (6.65)	29.12 (6.39)	29.27 (6.52)
Median	28.07	27.93	28.04
Min, Max	13.5, 56.3	11.3, 63.5	11.3, 63.5
BMI category			
≤30 kg/m^2	499 (62.7)	519 (64.0)	1018 (63.3)
>30 kg/m^2	297 (37.3)	292 (36.0)	589 (36.7)
Smoking status/Tobacco use			
Current smoker/tobacco user	104 (13.1)	113 (13.9)	217 (13.5)
Former smoker/tobacco user	203 (25.5)	224 (27.6)	427 (26.6)
Non-smoker/non-tobacco user	489 (61.4)	474 (58.4)	963 (59.9)

Characteristic	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)	Total N=1607 n (%)
Average Daily Alcohol Consumption			
0-1 drink/day	733 (92.1)	744 (91.7)	1477 (91.9)
2-3 drinks/day	59 (7.4)	63 (7.8)	122 (7.6)
≥4 drinks/day	4 (0.5)	4 (0.5)	8 (0.5)
Diabetes status			
Diabetic	60 (7.5)	65 (8.0)	125 (7.8)
Non-diabetic	736 (92.5)	746 (92.0)	1482 (92.2)

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 16, pp. 66-68.
N = number of subjects in the total group; n (%) = number and percent of subjects with the medical/behavioral characteristic; BMI = body mass index; max = maximum; min = minimum; SD = standard deviation

Reviewer comment: *No clinically significant between-group differences in the Safety Set, PPS, FAS, or SSA1 (data not shown) were identified. More than one-third of subjects in the Safety Set were obese. Although subjects with stable chronic medical conditions were eligible for enrollment, less than 10% of subjects were diabetic and only 13.5% were current smokers, both populations with lower seroprotective immune responses observed following HBV vaccines.*

The Applicant presented an analysis of medical history by vaccine group. The percentage of subjects with any medical history reported (Sci-B-Vac 87.4%; Engerix-B 87.1%) and medical history by System Organ Class (SOC) was similar between groups. The most commonly reported medical history findings by SOC were Musculoskeletal and connective tissue disorders (35.5%), surgical and medical procedures (34.3%), Immune system disorders (30.5%), and vascular disorders (30.1%). All of the reported PTs in the Immune system disorders SOC were related to allergies. The most common medical history findings by PT were hypertension (27.6%), seasonal allergy (17.3%), osteoarthritis (16.6%), and hypercholesterolemia (13.2%).

Reviewer comment: *No clinically significant between-group differences in medical history were identified.*

6.1.10.1.3 Subject Disposition
An overview of the analysis populations used for evaluation of safety and immunogenicity endpoints is provided below. A total of 2,472 screened subjects composed the All Enrolled Set. The ITT population, which included all randomized subjects, comprised 796 subjects in the Sci-B-Vac arm and 811 subjects in the Engerix-B arm. All randomized subjects received at least one dose of vaccine and thus, were included in the Safety Set.

Of 1,607 randomized and vaccinated subjects, 1,585 (98.6%) were included in the FAS (98.2% of the Sci-B-Vac arm and 99.0% in the Engerix-B arm). Of 1,607 randomized and vaccinated subjects, 1,447 (90.0%) subjects were included in the PPS (90.2% in the Sci-B-Vac arm and 89.9% in the Engerix-B arm).

Table 6. Analysis Populations, Sci-B-Vac-001, Intent-to-Treat

Analysis Population	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)	Total N=2472 n (%)
All Enrolled Set[a]			2472
Intent-to-Treat (ITT)[b]	796	811	1607
Safety Set[c]	796 (100.0)	811 (100.0)	1607 (100.0)
Full Analysis Set (FAS)[d]	782 (98.2)	803 (99.0)	1585 (98.6)
Per Protocol Set (PPS)[e]	718 (90.2)	729 (89.9)	1447 (90.0)
Clinical Laboratory Sub-study Analysis Set (SSA1)[f]	96 (12.1)	97 (12.0)	193 (12.0)

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 13, pp. 62-63.
Note: Percentages are based on the ITT population.
N = number of subjects in the total group; n (%) = number and percent of subjects in the analysis population
a All Enrolled Set included all screened subjects who provided informed consent and demographic and/or baseline screening assessments.
b ITT included all subjects in the All Enrolled Set who were randomized.
c Safety Set included all subjects in the All Enrolled Set who received at least one dose of vaccine.
d FAS included all subjects who received at least one dose of vaccine and provided at least one evaluable serum immunogenicity sample both at baseline and after baseline.
e PPS included all subjects in the FAS who received all three doses, had an evaluable serum immunogenicity sample at baseline and at the time point of interest, were seronegative at baseline, and had no major protocol violations leading to exclusion.
f Clinical Laboratory Sub-study (SSA1) Analysis Set included all subjects in the All Enrolled Set who received at least one dose of vaccine and participated in the clinical laboratory sub-study.

Reviewer comment: *The proportions of subjects in the ITT that were included in the FAS and PPS for the analyses of efficacy were comparable between treatment groups.*

Exposure

The table below shows the total number of vaccine doses received. Most subjects, 95.2% of the Sci-B-Vac arm and 96.8% of the Engerix-B, received three doses of vaccine.

Table 7. Number and Percentage of Subjects by Total Number of Vaccine Doses Received, Sci-B-Vac-001, Safety Set

Total Number of Doses Received	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
1 dose	17 (2.1)	10 (1.2)
2 doses	21 (2.6)	16 (2.0)
3 doses	758 (95.2)	785 (96.8)

Source: 125737/0.0, Sci-B-Vac-001 CSR, Table 29, p. 94.
N = number of subjects in the total group; n (%) = number and percent of subjects who received the specified total number of doses

Reviewer comment: *The proportion of subjects who completed the series is high in both groups (>95%), but slightly lower in the Sci-B-Vac group compared to the Engerix-B group. In a reviewer analysis stratified by age group, at least 92.4% of subjects in any age group received three doses of vaccine. A lower percentage of subjects who were 18-44 YOA received all three doses of Sci-B-Vac compared to Engerix-B (92.4% and 96.1%, respectively); all subjects in this age group discontinued for pregnancy or "other" reasons (see below).*

The table below presents the reasons for discontinuation of treatment.

Table 8. Discontinuations from Treatment, Sci-B-Vac-001, Safety Set

Reason for Discontinuation from Treatment	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Discontinued from treatment	38 (4.8)	26 (3.2)
Primary reason		
SAE	2 (0.3)	2 (0.2)
Non-serious AE*	4 (0.5)	3 (0.4)
Pregnancy	3 (0.4)	0
Other*	29 (3.6)	21 (2.6)

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 14, p. 63-64.
Note: Percentages are based on the number of subjects randomized and vaccinated.
N = number of subjects in the total group; n (%) = number and percent of subjects who discontinued treatment for the specified reason; SAE = serious adverse event; AE = adverse event
* One subject in the Sci-B-Vac group was classified by the investigator as discontinuing treatment for the "other" reason of "allergic reaction to vaccine," and is included here as discontinuing due to an AE.

Reviewer comment: *More subjects in the Sci-B-Vac arm than in the Engerix-B arm discontinued treatment for "Other" reasons. Other reasons included lost to follow-up (9 subjects, 1.1% in the Sci-B-Vac and 10 subjects, 1.2% in the Engerix-B groups) and withdrawal of consent (listed among the reasons for treatment discontinuation within the patient data listings for 10 subjects, 1.3% in the Sci-B-Vac group and 5 subjects, 0.6% in the Engerix-B group). One subject in the Sci-B-Vac group withdrew for an "other" reason of an allergic reaction to vaccine; this subject has been included in the table above and the reviewer's counts of treatment discontinuations due to an AE, but does not appear in the Applicant's counts as such. Another subject in the Sci-B-Vac group with a medical history of suspected ankylosing spondylitis withdrew due to starting sulfasalazine, a forbidden medication, for worsening back pain. One subject in the Engerix-B group withdrew consent because of unrelated SAEs of Aortic stenosis and Atrioventricular block second degree (listed as "Other" due to consent withdrawal in the table above). Please see 6.1.12.7 for a description of discontinuations due to adverse events. The remainder of the "other" reasons were reviewed and did not suggest vaccine-related AEs.*

Protocol deviations

Of 1,607 subjects vaccinated, 32.2% had at least one protocol deviation during the study that was classified by the Applicant as major (32.2% in both vaccine groups). The most common major protocol deviations were related to procedures or tests not performed in accordance with the protocol (323 subjects, 20.1%). This included an unblinding event at sites in Canada affecting 126 (15.8%) and 133 (16.4%) subjects in the Sci-B-Vac and Engerix-B groups, respectively. Major protocol deviations that led to exclusion from the PPS were reported in 42 subjects (5.3%) in the Sci-B-Vac group and 55 subjects (6.8%) in the Engerix-B group. The most common reason for exclusion from the PPS was out-of-window immunogenicity visits.

Reviewer comment: *The Applicant classified most missing protocol-specified procedures (for example, missing diary card information or vital signs) as major protocol deviations, and consequently a higher rate of major protocol deviations than would usually be expected is reported. The Applicant did not include subjects who discontinued treatment in the major protocol deviations leading to exclusion from PPS or FAS, though these subjects were not included in those analysis sets. The Applicant submitted details on the unblinding event in 125737.025, for which 2 of 13 clinical site staff (study coordinators at sites 105 and 114) confirmed opening email attachments with blinded*

information. The Applicant determined data integrity was not compromised as the incident occurred following the last subject last visit, all safety information being entered, and all source data being verified, and during a time when changes to the database were made only in response to data queries. The reviewer agrees with this assessment and that appropriate corrective actions were taken.

Disposition

Of the 1,607 subjects in the Safety Set, 82 subjects withdrew prior to completing the study (40 subjects, 5.0% in the Sci-B-Vac and 42 subjects, 5.2% in the Engerix-B groups). The table below shows subject disposition.

Table 9. Subject Disposition, Sci-B-Vac-001, Safety Set

Disposition	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Safety Set	796 (100.0)	811 (100.0)
Completed treatment	758 (95.2)	785 (96.8)
Discontinued from treatment	38 (4.8)	26 (3.2)
Completed Study	756 (95.0)	769 (94.8)
Withdrew prior to completing the study	40 (5.0)	42 (5.2)
Primary reason for early withdrawal from study		
SAE	1 (0.1)	0
Non-serious AE	0	3 (0.4)
Lost to follow-up	15 (1.9)	20 (2.5)
Consent withdrawal, not due to an AE	11 (1.4)	9 (1.1)
Other	6 (0.8)	3 (0.4)
Moved from the study area	2 (0.3)	3 (0.4)
Pregnancy	2 (0.3)	1 (0.1)
Investigator decision	1 (0.1)	1 (0.1)
Clinically significant change in subject's medical condition	0	1 (0.1)
Major protocol violation	1 (0.1)	0
Request of regulatory agency, or Sponsor or PI	1 (0.1)	0
Non-compliance with protocol	0	1 (0.1)

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 14, p. 63-64.
Note: Percentages are based on the number of subjects randomized and vaccinated.
N = number of subjects in the total group; n (%) = number and percent of subjects with the specified study or treatment status or who discontinued the study for the specified reason; SAE = serious adverse event; AE = adverse event; PI = principal investigator

The most common reasons for early discontinuation from the study were lost to follow-up (1.9% Sci-B-Vac and 2.5% Engerix-B) and withdrawal of consent (1.4% Sci-B-Vac and 1.1% Engerix-B).

Reviewer comment: *Most study subjects completed the study, and a similar percentage of subjects withdrew prior to completing the study in both treatment groups.*

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Co-primary endpoint 1: non-inferiority in subjects ≥18 years of age

The first co-primary endpoint was based on the PPS. The table below shows the results of this analysis. At Day 196, 4 weeks after the third dose, in 1,447 subjects in the PPS, the SPR was 91.4% in the Sci-B-Vac arm and 76.5% in the Engerix-B arm.

Table 10. Analysis of Seroprotection Rate at Day 196, Sci-B-Vac Compared to Engerix-B, Subjects ≥18 Years of Age, Sci-B-Vac-001, Per Protocol Set

Parameter	Sci-B-Vac N=718	Engerix-B N=729
Number of subjects evaluated	718	723
Number of subjects who achieved seroprotection	656	553
Seroprotection Rate, % (95% CI[a])	91.4 (89.1, 93.3)	76.5 (73.2, 79.5)
Estimated difference in SPR[b], % (95% CI)		14.9 (11.2, 18.6)

Source: Adapted from 125737/0.0 Sci-B-Vac-001 CSR, Table 19, p. 72.
Note: Seroprotection was defined as anti-HBs levels ≥10 mIU/mL in serum.
N = number of subjects in the total group; anti-HBs = hepatitis B surface ant body; CI = confidence interval; SPR = seroprotection rate
a Exact (Clopper-Pearson) two-sided CI based on the observed proportion of subjects.
b The estimated difference in proportions [SPR(Sci-B-Vac)-SPR(Engerix-B)] and two-sided 95% CIs were calculated using the Miettinen and Nurminen method.

As the LB of the 95% CI of the difference in SPR (Sci-B-Vac−Engerix-B) was 11.2%, which was greater than the preset margin of -5%, non-inferiority of Sci-B-Vac compared with Engerix-B at Day 196 in subjects ≥18 YOA was demonstrated, and the first co-primary endpoint was met.

Reviewer comment: *Although cross-study comparisons can't be made, the SPR in the Engerix-B group was slightly lower than expected and described in the Engerix-B prescribing information, which includes one study with SPR point estimates of 75% in adults with diabetes and 82% in matched non-diabetic controls following Engerix-B vaccination. The CDC reports that vaccination with a complete series results in seroprotection in >90% of healthy adults aged <40 YOA and in 75% of persons ≥60 YOA (Schillie, 2018). There may be differences in baseline medical and demographic characteristics contributing to the slightly lower SPR of Engerix-B in this study.*

The Applicant presented sensitivity analyses in subjects in the FAS, including and excluding subjects who were seroprotected pre-vaccination. These results were similar to the PPS analysis.

Twenty-six subjects (3.6%) in the Sci-B-Vac group and 20 subjects (2.7%) in the Engerix-B group in the PPS had anti-HBs titers >1,000 mIU/mL 4 weeks after administration of the first dose (Day 28). Of these subjects, 6 in the Sci-B-Vac group and 2 in the Engerix-B group had indeterminate values of anti-HBs (>4.23 and <10.0 mIU/mL) on the VITROS assay at Day 1 despite negative HBV serology at screening, and 20 subjects in the Sci-B-Vac group and 18 subjects in the Engerix-B group had undetectable levels of anti-HBs at screening and prior to vaccination on Day 1 (using the VITROS assay). In 125737/0.19, the Applicant postulated that the high titers observed 4 weeks after the first dose may be the result of previously unrecognized prior exposure or immunization against HBV several decades prior to study enrollment.

Reviewer comment: *Anamnestic responses in previously vaccinated subjects have been demonstrated decades following the primary series (Bruce, 2016). A small and similar percentage of subjects in each vaccination group had a robust and early response, potentially suggesting prior vaccination or exposure.*

Co-primary endpoint 2: superiority in subjects ≥45 years of age

The second co-primary endpoint was based on subjects 45 YOA and older in the FAS who were seronegative at baseline (subjects who were enrolled in the study but found to be seropositive on the day of first vaccination were included in the FAS but excluded from this analysis). The table below shows the results of this analysis. At Day 196, 4 weeks after the third dose, in 1,252 subjects ≥45 years of age in the FAS, the SPR was 89.4% in the Sci-B-Vac arm and 73.1% in the Engerix-B arm.

Table 11. Analysis of Seroprotection Rate at Day 196, Sci-B-Vac Compared to Engerix-B, Subjects ≥45 Years of Age Excluding Those Seropositive at Baseline, Sci-B-Vac, Full Analysis Set

Parameter	Sci-B-Vac N=638	Engerix-B N=646
Number of subjects evaluated	625	627
Number of subjects who achieved seroprotection	559	458
Seroprotection rate, % (95% CI[a])	89.4 (86.8, 91.7)	73.1 (69.4, 76.5)
Estimated difference in SPR[b], % (95% CI)		16.4 (12.2, 20.7)

Source: Adapted from 125737/0.0 Sci-B-Vac-001 CSR, Table 21, p. 77.
Note: Seroprotection was defined as anti-HBs levels ≥10 mIU/mL in serum
N = number of subjects in the total group; anti-HBs = hepatitis B surface ant body; CI = confidence interval; SPR = seroprotection rate
a Exact (Clopper-Pearson) two-sided CI based on the observed proportion of subjects
b The estimated difference in proportions [SPR(Sci-B-Vac)-SPR(Engerix-B)] and two-sided 95% CIs were calculated using the Miettinen and Nurminen method

As the LB of the 95% CI of the difference in SPR (Sci-B-Vac−Engerix-B) was 12.2%, which was greater than the Applicant's preset margins of >0% to declare statistical superiority and >5% to declare clinical superiority, the second co-primary endpoint was met.

Reviewer comment: *In subjects ≥45 YOA, 89.4% of Sci-B-Vac recipients compared to 73.1% of Engerix-B recipients achieved anti-HBs ≥10 mIU/mL. While the specified seroresponse threshold is generally accepted as evidence of protection, immune responses beyond those related to anti-HBs antibody may contribute to protection in this population, and thus differences in SPR do not necessarily indicate clinically meaningful differences in vaccine effectiveness. The SPRs in both study arms were similar to the total study population, likely because 80% of the study population is ≥45 YOA.*

6.1.11.2 Analyses of Secondary Endpoints

Secondary endpoints were assessed sequentially. The first secondary endpoint was to assess the non-inferiority of the SPR on Day 168, 20 weeks following the second dose and prior to the third dose, in the Sci-B-Vac arm compared to the SPR on Day 196, one month after the third dose, in the Engerix-B arm. This analysis was conducted on all subjects ≥18 YOA in the PPS. The table below shows the results of this analysis. At Day 168, in a total of 1,440 subjects in the PPS, the SPR was 66.0% in the Sci-B-Vac arm and at Day 196, the SPR was 76.5% in the Engerix-B arm.

Table 12. Analysis of the Seroprotection Rate, Day 168 Sci-B-Vac Compared to Day 196 Engerix-B, Subjects ≥18 Years of Age, Sci-B-Vac-001, Per Protocol Set

Parameter	Sci-B-Vac N=718	Engerix-B N=729
Number of subjects evaluated	717	723
Number of subjects who achieved seroprotection	473	553
Seroprotection Rate, % (95% CI[a])	66.0 (62.4, 69.4)	76.5 (73.2, 79.5)
Estimated difference in SPR[b], % (95% CI)		-10.5 (-15.2, -5.9)

Source: Adapted from 125737/0.0 Sci-B-Vac-001 CSR, Table 23, p. 80.
Note: Seroprotection was defined as anti-HBs levels ≥10 mIU/mL in serum.
N = total number of subjects in the group; anti-HBs = hepatitis B surface ant body; CI = confidence interval; SPR = seroprotection rate
a Exact (Clopper-Pearson) two-sided CI based on the observed proportion of subjects.
b The estimated difference in proportions [SPR(Sci-B-Vac)-SPR(Engerix-B)] and two-sided 95% CIs were calculated using the Miettinen and Nurminen method.

As the LB of the 95% CI of the difference in SPR (Sci-B-Vac−Engerix-B) was -15.2%, which was less than the preset margin of >−5%, the non-inferiority of Sci-B-Vac at Day 168 compared with Engerix-B at Day 196 was not demonstrated. Thus, the second secondary endpoint (non-inferiority of Sci-B-Vac at Day 56, compared to Engerix-B at Day 196) was not assessed.

Reviewer comment: *These results support the need for a third dose of Sci-B-Vac in adults ≥18 YOA. Results for the FAS analysis (including and excluding subjects who were seropositive at baseline) were consistent with the PPS analysis.*

6.1.11.3 Subpopulation Analyses

The table below presents the SPR at Day 196, 4 weeks after the third dose of vaccine, in demographic and clinical subpopulations of interest.

Table 13. Seroprotection Rate Day 196, 4 Weeks Following the Third Dose of Sci-B-Vac or Engerix-B in Subjects ≥18 Years of Age by Subgroup, Sci-B-Vac-001, Per Protocol Set

Subgroup	Sci-B-Vac N	Sci-B-Vac n	Sci-B-Vac SPR (%)	Sci-B-Vac 95% CI	Engerix-B N	Engerix-B n	Engerix-B SPR (%)	Engerix-B 95% CI
Age group (yrs)								
18-44	125	124	99.2	95.6, 100.0	135	123	91.1	85.0, 95.3
45-64	325	308	94.8	91.8, 96.9	322	258	80.1	75.3, 84.3
≥65	268	224	83.6	78.6, 87.8	266	172	64.7	58.6, 70.4
Age category (yrs)								
18-39	71	71	100.0	94.9, 100.0	72	67	93.1	84.5, 97.7
40-49	158	156	98.7	95.5, 99.9	143	128	89.5	83.3, 94.0
50-59	153	142	92.8	87.5, 96.4	164	128	78.1	70.9, 84.1
60-69	221	197	89.1	84.3 92.9	229	165	72.1	65.8, 77.8
≥70	115	90	78.3	69.6, 85.4	115	65	56.5	47.0, 65.7
Gender								
Male	282	245	86.9	82.4, 90.6	269	187	69.5	63.6, 75.0
Female	436	411	94.3	91.7, 96.3	454	366	80.6	76.7, 84.2
Race								
White	648	596	92.0	89.6, 94.0	660	506	76.7	73.3, 79.8
Black/ African American	57	49	86.0	74.2, 93.7	51	39	76.5	62.5, 87.2
Other	13	11	84.6	54.6, 98.1	12	8	66.7	34.9, 90.0
Ethnicity								
Hispanic/Latino	67	60	89.6	79.7, 95.7	65	45	69.2	56.6, 80.1
Not Hispanic/Latino	648	593	91.5	89.1, 93.5	655	505	77.1	73.7, 80.3

Subgroup	Sci-B-Vac N	Sci-B-Vac n	Sci-B-Vac SPR (%)	Sci-B-Vac 95% CI	Engerix-B N	Engerix-B n	Engerix-B SPR (%)	Engerix-B 95% CI
Country/Region								
United States	297	255	85.9	81.4, 89.6	304	205	67.4	61.9, 72.7
Canada	119	116	97.5	92.8, 99.5	120	99	82.5	74.5, 88.8
Europe	302	285	94.4	91.1, 96.7	299	249	83.3	78.6, 87.3
Diabetic Status								
Diabetes	54	45	83.3	70.7, 92.1	60	35	58.3	44.9, 70.9
No diabetes	664	611	92.0	89.7, 94.0	663	518	78.1	74.8, 81.2
BMI (kg/m^2)								
>30	269	240	89.2	84.9, 92.7	254	173	68.1	62.0, 73.8
≤30	449	416	92.7	89.8, 94.9	469	380	81.0	77.2, 84.5
Daily alcohol consumption[a]								
0-1 drinks	663	603	91.0	88.5, 93.0	662	510	77.0	73.6, 80.2
2-3 drinks	51	51	100.0	93.0, 100.0	57	40	70.2	56.6, 81.6
Smoking status								
Current smoker	92	79	85.9	77.1, 92.3	95	67	70.5	60.3, 79.4
Past smoker	187	167	89.3	84.0, 93.3	198	153	77.3	70.8, 82.9
Non-smoker	439	410	93.4	90.7, 95.5	430	333	77.4	73.2, 81.3

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 20, pp. 74-75.
Note: Seroprotection was defined as anti-HBs levels ≥10 mIU/mL in serum.
N = total number of subjects evaluated in each group; n = number of subjects who achieved seroprotection;
SPR = seroprotection rate; CI = confidence interval; anti-HBs = hepatitis B surface ant body; BMI = body mass index
a The subgroup of ≥4 drinks is not included as the number of subjects contr buting to this category was <5 in each treatment arm

Reviewer comment: *No multiplicity adjustments were made for subgroup analyses and some subgroups were too small to yield precise estimates or adequate power for hypothesis testing, which was not pre-specified. Therefore, results of these analyses should be interpreted with caution. Sci-B-Vac induced effective immune responses (SPR point estimates >78%) at Day 196 for all subgroups evaluated. CIs were wide and overlapping between vaccine groups for diabetics and current smokers, two populations of interest who did not make up a large proportion of the study population. For other subgroups (for example, ≥40 YOA, both genders, obese subjects) SPRs following Sci-B-Vac were higher than following Engerix-B. Overall, the subgroup analyses suggest the differences in SPR were consistent across subgroups.*

A lower SPR was observed in the US compared to Canada and Europe for both Sci-B-Vac and Engerix-B, although the SPR in the US was higher in the Sci-B-Vac group (85.9%) compared to the Engerix-B group (67.4%).

6.1.11.4 Dropouts and/or Discontinuations

The first co-primary analysis, which was the basis for licensure, was conducted in the PPS. The PPS included 90.0% of the subjects who received at least one dose of vaccine (Safety Set). Results of first co-primary immunogenicity analyses performed in the FAS were consistent with those performed in the PPS.

6.1.11.5 Exploratory and Post Hoc Analyses

The table below shows the SPR at specified time points during the study. The SPR peaked in the Sci-B-Vac group at 91.4% at Day 196, 4 weeks after the third dose, and remained high (89%) at Day 336, approximately 6 months after the third dose.

Table 14. Seroprotection Rate at Days 28, 56, 168, 196, and 336, Subjects ≥18 Years of Age, Sci-B-Vac-001, Per Protocol Set

Study Day	Sci-B-Vac N	Sci-B-Vac n	Sci-B-Vac SPR (95% CI[a])	Engerix-B N	Engerix-B n	Engerix-B SPR (95% CI[a])
28	717	115	16.0 (13.4, 18.9)	728	56	7.7 (5.9, 9.9)
56	717	369	51.5 (47.7, 55.2)	728	174	23.9 (20.9, 27.2)
168	717	473	66.0 (62.4, 69.4)	729	200	27.4 (24.2, 30.8)
196	718	656	91.4 (89.1, 93.3)	723	553	76.5 (73.2, 79.5)
336	709	631	89.0 (86.5, 91.2)	715	492	68.8 (65.3, 72.2)

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 24, p. 82.
Note: Seroprotection was defined as anti-HBs levels ≥10 mIU/mL in serum.
N = total number of subjects evaluated in each group; n = number of subjects who achieved seroprotection; anti-HBs = hepatitis B surface antibody; CI = confidence interval; SPR = seroprotection rate
a Exact (Clopper-Pearson) two-sided CI based on the observed proportion of subjects.
b The estimated difference in proportions [SPR(Sci-B-Vac®)-SPR(Engerix-B)] and two-sided 95% CIs were calculated using the Miettinen and Nurminen method.

The table below shows the GMCs in each vaccine group at specified time points during the study. In the Sci-B-Vac group, the GMC peaked at 1,148.31 mIU/mL at Day 196 and remained above the seroprotective level at Day 336, 6 months later. In the Engerix-B group, the GMC peaked at 192.65 mIU/mL at Day 196 and was 69.24 mIU/mL at Day 336.

Table 15. Anti-HBs GMC (mIU/mL) at Days 28, 56, 168, 196, and 336 in Subjects ≥18 Years of Age, Sci-B-Vac-001, Per Protocol Set

Study Day	Sci-B-Vac N=718 n	Sci-B-Vac N=718 GMC	Engerix-B N=729 n	Engerix-B N=729 GMC
28	717	4.57	728	3.24
56	717	17.25	728	5.85
168	717	27.61	729	5.82
196	718	1148.31	723	192.65
336	709	445.07	715	69.24

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 26, p. 87.
N = total number of subjects in each group; n = number of subjects evaluated; GMC = geometric mean concentration

Reviewer comment: *The clinical benefit of higher anti-HBs titers (beyond the seroprotective level) and the persistence of anti-HBs above the seroprotective level have not been established in the general population, and immunocompetent individuals who initially respond to HBV vaccination are considered protected even if anti-HBs levels fall below 10 mIU/mL (Schillie, 2018).*

6.1.12 Safety Analyses

6.1.12.1 Methods

Descriptive safety analyses were conducted on the Safety Set, all subjects who received at least one dose of vaccine. Please see section 6.1.7 for a description of active and passive safety monitoring.

6.1.12.2 Overview of Adverse Events

The Safety Set, the primary population for the assessment of safety, included 1,607 subjects total, 796 in the Sci-B-Vac group and 811 in the Engerix-B group.

Solicited adverse events

Compliance with local, systemic, and other (vital signs, including fever) solicited AE assessments in the 30-minute post-vaccination period was ≥99.5% of subjects vaccinated in each treatment group for each vaccine dose. Compliance with diary card assessments of local, systemic, and other solicited AEs on Day 1 (after the 30-minute post-vaccination assessment) and Days 2 through 7 was ≥97.4% of subjects vaccinated in each treatment group for each vaccine dose.

Reviewer comment: *Because the protocol specified collection of solicited local, systemic and other AEs in the 30-minute post-vaccination period and all subjects had this assessment following the first dose, all subjects in the Safety Set had post-vaccination safety data collected. The Applicant presented solicited AEs based on the total number of subjects vaccinated (Safety Set). As diary card completion rates were high, there were minimal differences between percentages of solicited AEs in the Safety Set and percentages among subjects who returned diary cards.*

Solicited local AEs: Overall by subject, all doses considered, at least one solicited local AE was reported by 71.9% and 46.7% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. At least one ≥ Grade 3 solicited local AE was reported by 1.6% of subjects in both the Sci-B-Vac and Engerix-B groups. The numbers and proportions of subjects in the Safety Set reporting any grade and ≥ Grade 3 solicited local AEs are shown below.

Table 16. Incidence of Solicited Local Adverse Events and Maximum Severity Grade 3 and 4 Solicited Local Adverse Events Reported Day 1 Through Day 7 Following Any Dose, Overall by Subject, Sci-B-Vac-001, Safety Set

Solicited Local Adverse Event Severity (Grade)	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Any Solicited Local Adverse Event		
Any Grade	572 (71.9)	379 (46.7)
Severe (3)	10 (1.3)	5 (0.6)
Potentially life-threatening (4)*	3 (0.4)	8 (1.0)
Pain		
Any Grade	503 (63.2)	294 (36.3)
Severe (3)	1 (0.1)	1 (0.1)
Potentially life-threatening (4)	0	0
Tenderness		
Any Grade	484 (60.8)	282 (34.8)
Severe (3)	8 (1.0)	3 (0.4)
Potentially life-threatening (4)	0	0
Pruritus/itching		
Any Grade	76 (9.5)	66 (8.1)
Severe (3)	1 (0.1)	2 (0.2)
Potentially life-threatening (4)	0	0
Redness/erythema		
Any Grade	18 (2.3)	15 (1.8)
Severe (3)	0	0
Potentially life-threatening (4)*	2 (0.3)	7 (0.9)

Solicited Local Adverse Event Severity (Grade)	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Swelling/edema		
Any Grade	18 (2.3)	12 (1.5)
Severe (3)	0	3 (0.4)
Potentially life-threatening (4)*	2 (0.3)	1 (0.1)

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 32, p. 102 and Table 34, pp. 102-103.
N = number of subjects who received at least one documented dose; n (%) = number and percent of subjects reporting the adverse event at least once

* Reports of Grade 4/potentially life-threatening erythema and swelling were based on the subject-reported presence of skin necrosis "death of skin cells" or exfoliative dermatitis "peeling over large areas of the skin" at the injection site, while the actual measurement of erythema and edema would be classified as Grade 0 to Grade 1.

Overall by subject, all doses considered, pain and tenderness were the most frequently reported local solicited AEs. IS pain was reported by 63.2% and 36.3% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. IS tenderness was reported by 60.8% and 34.8% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. Grade 3 injection site pain and tenderness were uncommon (≤1% of subjects) in both study groups.

Reviewer comment: *Local solicited reactogenicity was notably more common in the Sci-B-Vac group, in particular IS pain and tenderness. Severe local reactogenicity was reported in more subjects in the Sci-B-Vac group but was uncommon in both groups. In both groups, the percentage of subjects reporting solicited local reactogenicity was highest following the first dose and was lower following subsequent doses (data not shown, Sci-B-Vac dose 1: 57.7%, dose 2: 49.9%, dose 3: 47.4%).*

A total of 12 Grade 4 solicited local AEs were reported in 11 subjects; 3 Sci-B-Vac recipients reported 4 events and 8 Engerix-B recipients reported 8 events. Redness/erythema accounted for 9 Grade 4 solicited AEs (2 Sci-B-Vac recipients; 7 Engerix-B recipients) and swelling/edema accounted for 3 Grade 4 solicited AEs (2 Sci-B-Vac recipients; 1 Engerix-B recipient). Grade 4 local reactogenicity was reported following the first (2 Sci-B-Vac recipients; 3 Engerix-B recipients), second (0 Sci-B-Vac recipients; 2 Engerix-B recipients) and third dose (2 Sci-B-Vac recipients; 3 Engerix-B recipients). As per the Applicant, these events were assigned a severity of Grade 4 based on the subject checking a box on the diary card indicating the presence of exfoliative dermatitis and/or skin necrosis at the injection site. The recorded measurements of the maximum diameter of erythema or swelling during the post-vaccination period in which exfoliative dermatitis and/or skin necrosis was noted were 0 to 30 mm; by measurement the highest severity would be Grade 1. None of the Grade 4 solicited local AEs were medically attended and no medical treatment was reported. All these events resolved with no sequelae. Subjects who reported a Grade 4 solicited AE following dose 1 or 2, completed the three-dose series with no recurrence of Grade 4 events.

Reviewer comment: *The Applicant responded to multiple queries about these events. There is no indication of relationship of Grade 4 local reactogenicity to vaccine group or dose number. In all cases, subjects did not report to the study site the occurrence of concerning local reactogenicity soon after vaccination, except via the completed diary card upon return to the study site 28 days later. Furthermore, one may reasonably expect additional reports of Grade 3 solicited local AEs of redness and swelling if vaccination was associated with exfoliative dermatitis or skin necrosis; there were no*

reports of Grade 3 redness or swelling in the Sci-B-Vac group and 3 subjects with Grade 3 swelling in the Engerix-B group. The reports of grade 4 events appear to be the result of a combination of the following potential issues: the Applicant allowing subjects to categorize reactogenicity as Grade 4, study sites not adequately training at least some subjects on completion of the diary card, and the Applicant not instructing investigators to assess and reconcile these Grade 4 events and/or choosing not to record investigator assessments of solicited AEs in the datasets when their assessment differed from the subjects', as is allowed by CBER if documented appropriately in the datasets (IND 17542, CBER communications dated February 12, 2020 and March 11, 2020). Based on the information provided, it is not anticipated that these reports of Grade 4 local reactogenicity present a safety concern.

No subject in the Sci-B-Vac group reported redness or swelling >10.0 cm. No local solicited AEs in the Sci-B-Vac arm were assessed as medically attended.

The table below shows the number and proportion of subjects in both groups reporting solicited local adverse events (any grade and maximum grade 3 and 4) by age group.

Table 17. Incidence of Solicited Local Adverse Events Reported Day 1 Through Day 7 Following Each Dose of Vaccine, by Age Group, Overall by Subject, Sci-B-Vac-001, Safety Set

Solicited Local Adverse Event Severity (Grade)	Sci-B-Vac 18-44 YOA N=145 n (%)	Engerix-B 18-44 YOA N=154 n (%)	Sci-B-Vac 45-64 YOA N=355 n (%)	Engerix-B 45-64 YOA N=361 n (%)	Sci-B-Vac ≥65 YOA N=296 n (%)	Engerix-B ≥65 YOA N=296 n (%)
Any Solicited Local Adverse Event	117 (80.7)	99 (64.3)	271 (76.3)	175 (48.5)	184 (62.2)	105 (35.5)
Severe (3)	2 (1.4)	3 (1.9)	8 (2.3)	1 (0.3)	0	1 (0.3)
Potentially life-threatening (4)*	0	1 (0.6)	1 (0.3)	6 (1.7)	2 (0.7)	1 (0.3)
Pain	108 (74.5)	80 (51.9)	238 (67.0)	133 (36.8)	157 (53.0)	81 (27.4)
Severe (3)	0	0	1 (0.3)	0	0	1 (0.3)
Potentially life-threatening (4)	0	0	0	0	0	0
Tenderness	102 (70.3)	77 (50.0)	225 (63.4)	134 (37.1)	157 (53.0)	71 (24.0)
Severe (3)	2 (1.4)	2 (1.3)	6 (1.7)	1 (0.3)	0	0
Potentially life-threatening (4)	0	0	0	0	0	0
Pruritus/itching	13 (9.0)	20 (13.0)	30 (8.5)	28 (7.8)	33 (11.1)	18 (6.1)
Severe (3)	0	2 (1.3)	1 (0.3)	0	0	0
Potentially life-threatening (4)	0	0	0	0	0	0
Redness/erythema	3 (2.1)	3 (1.9)	9 (2.5)	9 (2.5)	6 (2.0)	3 (1.0)
Severe (3)	0	0	0	0	0	0
Potentially life-threatening (4)*	0	0	0	6 (1.7)	2 (0.7)	1 (0.3)
Swelling/edema	5 (3.4)	4 (2.6)	8 (2.3)	3 (0.8)	5 (1.7)	5 (1.7)
Severe (3)	0	2 (1.3)	0	0	0	1 (0.3)
Potentially life-threatening (4)*	0	1 (0.6)	1 (0.3)	0	1 (0.3)	0

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 35, pp. 104-105.
YOA = years of age; N = number of subjects who received at least one documented dose in the age group; n (%) = number and percent of subjects reporting the adverse event at least once
* Reports of Grade 4/potentially life-threatening erythema and swelling were based on the subject-reported presence of skin necrosis "death of skin cells" or exfoliative dermatitis "peeling over large areas of the skin" at the injection site, while the actual measurement of erythema and edema would be classified as Grade 0 to Grade 1.

Reviewer comment: *A majority of subjects who received Sci-B-Vac in each age group reported local solicited AEs. Within each age group, solicited local reactogenicity was reported more frequently in the Sci-B-Vac group compared to the Engerix-B group. Percentages of subjects reporting pain and tenderness, the most commonly reported solicited local symptoms, tended to decrease with increasing age group, particularly in*

subjects ≥65. This age-associated decline in solicited local reactogenicity was more notable in the Engerix-B group. Among subjects ≥65 YOA, Sci-B-Vac recipients were nearly twice as likely to report local reactogenicity as Engerix-B recipients. In all age groups, local reactogenicity following Sci-B-Vac tended to decrease with subsequent doses, driven by pain and tenderness.

Overall, considering all doses, the median durations of pain, tenderness, pruritus, redness, and swelling reported after Sci-B-Vac administration were 2.0, 2.0, 1.5, 1.0, and 2.0 days, respectively. In the Sci-B-Vac group, 16 subjects (2.0%) reported IS pain continuing beyond the 7-day assessment period (median duration 9.0 days) and three subjects (0.4%) reported IS pruritus continuing beyond the 7-day assessment period (median duration 14.0 days).

Solicited systemic AEs: Overall by subject, all doses considered, at least one solicited systemic AE was reported by 55.9% and 49.0% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. At least one ≥ Grade 3 solicited systemic AE was reported by 1.8% and 2.5% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. The number and proportion of subjects in the Safety Set reporting any grade and ≥ Grade 3 solicited systemic AEs are shown below.

Table 18. Incidence of Solicited Systemic Adverse Events and Maximum Severity Grade 3 and 4 Solicited Systemic Adverse Events Reported Day 1 Through Day 7 Following Each Dose of Vaccine, Overall by Subject, Sci-B-Vac-001, Safety Set

Solicited Systemic Adverse Event Severity (Grade)	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Any Systemic		
Any	445 (55.9)	397 (49.0)
Severe (3)	13 (1.6)	20 (2.5)
Potentially life-threatening (4)*	1 (0.1)	0
Nausea/vomiting		
Any	56 (7.0)	73 (9.0)
Severe (3)	1 (0.1)	3 (0.4)
Potentially life-threatening (4)	0	0
Diarrhea		
Any	82 (10.3)	96 (11.8)
Severe (3)	2 (0.3)	2 (0.2)
Potentially life-threatening (4)	0	0
Headache		
Any	249 (31.3)	238 (29.3)
Severe (3)	4 (0.5)	6 (0.7)
Potentially life-threatening (4)	0	0
Fatigue		
Any	242 (30.4)	249 (30.7)
Severe (3)	5 (0.6)	13 (1.6)
Potentially life-threatening (4)*	1 (0.1)	0
Myalgia		
Any	276 (34.7)	197 (24.3)
Severe (3)	3 (0.4)	3 (0.4)
Potentially life-threatening (4)	0	0

Solicited Systemic Adverse Event Severity (Grade)	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Fever		
Any	6 (0.8)	9 (1.1)
Severe (3)	1 (0.1)	1 (0.1)
Potentially life-threatening (4)	0	0

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 38, pp. 108-109, Table 40, pp. 109-110, and Table 14.3.1.13.3, pp. 18114-18129.
N = number of subjects who received at least one documented dose; n (%) = number and percent of subjects reporting the adverse event at least once
* One event of Grade 4 fatigue may have been inappropriately categorized.

Overall by subject, all doses considered, myalgia, headache, and fatigue were the most frequently reported systemic solicited AEs. Any grade myalgia (≥ Grade 3 myalgia) was reported by 34.7% (0.4%) and 24.7% (0.4%) of subjects in the Sci-B-Vac and Engerix-B groups, respectively. Any grade headache (≥ Grade 3 headache) was reported by 31.3% (0.5%) and 29.3% (0.7%) of subjects in the Sci-B-Vac and Engerix-B groups, respectively. Any grade fatigue (≥ Grade 3 fatigue) was reported by 30.4% (0.7%) and 30.7% (1.6%) of subjects in the Sci-B-Vac and Engerix-B groups, respectively. Fever of any grade was uncommon.

Reviewer comment: *Systemic solicited reactogenicity was slightly more common in the Sci-B-Vac group compared to the Engerix-B group. Myalgia was the only systemic solicited AE reported clinically significantly more frequently in the Sci-B-Vac group compared to the Engerix-B group. Otherwise, the systemic reactogenicity of the two vaccines was comparable. Severe systemic reactogenicity was uncommon. Fever was uncommon. The percentage of subjects in the Sci-B-Vac group reporting solicited systemic reactogenicity was highest following the first dose (data not shown, Sci-B-Vac dose 1: 41.0%, dose 2: 31.5%, dose 3: 28.4%). This was generally true for each solicited AE.*

One Grade 4 solicited systemic AE was reported. A 41-year-old woman reported Grade 4 fatigue beginning the day after dose 2 of Sci-B-Vac and lasting for 23 days. This event was reported concurrently with severe bronchitis, which began 5 days post-dose 2. The unsolicited AE of bronchitis was medically attended, requiring a doctor's visit. The investigator assessed the unsolicited AE of fatigue, the solicited AE that extended beyond the assessment period, as severe and assessed both the fatigue and bronchitis as unrelated. The subject received the third dose of Sci-B-Vac as scheduled with no recurrence of fatigue.

Reviewer comment: *The AE of fatigue appears to have been inappropriately categorized as Grade 4 as the Applicant has no record that the subject required an ER visit or hospitalization.*

Solicited systemic AEs in 1 (0.1%) subject in the Sci-B-Vac group and 3 (0.5%) subjects in the Engerix-B group were medically attended. In the Sci-B-Vac group, a 60-year-old woman reported a moderate fever to 38.9°C the day after dose 1. It resolved the following day, and she received two additional doses without recurrence of fever.

The table below shows the number and proportion of subjects in both groups reporting solicited systemic adverse events (any grade and maximum Grade 3 and 4) by age group.

Table 19. Incidence of Solicited Systemic Adverse Events Reported Day 1 Through Day 7 Following Any Dose, by Age Group, Overall by Subject, Sci-B-Vac-001, Safety Set

Solicited Systemic Adverse Event Severity (Grade)	Sci-B-Vac 18-44 YOA N=145 n (%)	Engerix-B 18-44 YOA N=154 n (%)	Sci-B-Vac 45-64 YOA N=355 n (%)	Engerix-B 45-64 YOA N=361 n (%)	Sci-B-Vac ≥65 YOA N=296 n (%)	Engerix-B ≥65 YOA N=296 n (%)
Any Solicited Systemic Adverse Event	106 (73.1)	89 (57.8)	212 (59.7)	186 (51.5)	127 (42.9)	122 (41.2)
Severe (3)	7 (4.8)	8 (5.2)	5 (1.4)	8 (2.2)	1 (0.3)	4 (1.4)
Potentially life-threatening (4)*	1 (0.7)	0	0	0	0	0
Nausea/vomiting	18 (12.4)	24 (15.6)	25 (7.0)	37 (10.2)	13 (4.4)	12 (4.1)
Severe (3)	1 (0.7)	1 (0.6)	0	0	0	2 (0.7)
Potentially life-threatening (4)	0	0	0	0	0	0
Diarrhea	21 (14.5)	23 (14.9)	32 (9.0)	43 (11.9)	29 (9.8)	30 (10.1)
Severe (3)	1 (0.7)	1 (0.6)	0	0	1 (0.3)	1 (0.3)
Potentially life-threatening (4)	0	0	0	0	0	0
Headache	74 (51.0)	63 (40.9)	123 (34.6)	117 (32.4)	52 (17.6)	58 (19.6)
Severe (3)	3 (2.1)	3 (1.9)	1 (0.3)	3 (0.8)	0	0
Potentially life-threatening (4)	0	0	0	0	0	0
Fatigue	63 (43.4)	64 (41.6)	107 (30.1)	109 (30.2)	72 (24.3)	76 (25.7)
Severe (3)	2 (1.4)	5 (3.2)	3 (0.8)	5 (1.4)	0	3 (1.0)
Potentially life-threatening (4)*	1 (0.7)	0	0	0	0	0
Myalgia	63 (43.4)	45 (29.2)	132 (37.2)	93 (25.8)	81 (27.4)	59 (19.9)
Severe (3)	1 (0.7)	2 (1.3)	2 (0.6)	0	0	1 (0.3)
Potentially life-threatening (4)	0	0	0	0	0	0
Fever	2 (1.4)	3 (1.9)	2 (0.6)	4 (1.1)	2 (0.7)	2 (0.7)
Severe (3)	1 (0.7)	0	0	1 (0.3)	0	0
Potentially life-threatening (4)	0	0	0	0	0	0

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 41, pp. 111-112, Table 14.3.1.15.3, pp. 18178-18193, and reviewer-generated analysis based on integrated dataset ADREACT.
YOA = years of age; N = number of subjects who received at least one documented dose in the age group; n (%) = number and percent of subjects reporting the adverse event at least once
* One event of Grade 4 fatigue may have been inappropriately categorized.

Reviewer comment: *For both vaccines, younger subjects reported more systemic reactogenicity. This pattern was more pronounced in the Sci-B-Vac group, in which 73.1% of subjects 18-45 YOA compared to 42.9% of subjects ≥65 YOA reported solicited systemic AEs. Myalgia was more frequently reported in the Sci-B-Vac group in all age groups. In the youngest age group (18-45 YOA), headache was also reported more frequently in the Sci-B-Vac group compared to the Engerix-B group. The solicited reactogenicity profile in the ≥65 YOA group was similar between Sci-B-Vac and Engerix-B, with the exception of any grade myalgias, which were reported more frequently in the Sci-B-Vac group.*

Overall, considering all doses, the median durations of myalgia, headache, fatigue, diarrhea, nausea/vomiting, and fever reported after Sci-B-Vac administration were 2.0, 1.0, 2.0, 2.0, 1.0, and 1.5 days, respectively. The most common solicited AEs continuing beyond the 7-day assessment period in the Sci-B-Vac group were fatigue (4.1%, 9.0 days median duration), headache (1.9%, 7.0 days median duration), and myalgia (1.9%,

9.0 days median duration). The proportion of subjects reporting each solicited systemic AEs extending beyond the 7-day assessment period was similar in the Engerix-B group.

Reviewer comment: *In general, solicited systemic AEs following Sci-B-Vac resolved after a short duration.*

Unsolicited adverse events

Unsolicited AEs were recorded by all subjects on a diary card, as well as during study visits and the safety phone calls, for 28 days (Days 1-28) following each dose of study vaccine. The Applicant presented serious and non-serious unsolicited AEs together. Solicited AEs that extended beyond the assessment period were also included as unsolicited AEs. An overview of unsolicited AEs is presented in the table below and detailed analysis of all unsolicited AEs follows. See section 6.1.12.4 for the analyses of SAEs.

Table 20. Overview of Unsolicited Adverse Events Day 1 to End of Study (Day 336) Unless Otherwise Specified, Sci-B-Vac-001, Safety Set

Adverse Event	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Unsolicited AE within 28 days of vaccination	369 (46.4)	389 (48.0)
Unsolicited vaccine-related AE within 28 days of any vaccination*	122 (15.3)	99 (12.2)
MAAE through Day 336	202 (25.4)	231 (28.5)
NOCI (investigator-determined) through Day 336	26 (3.3)	30 (3.7)
AE/SAE leading to treatment discontinuation†	6 (0.8)	5 (0.6)
Vaccine-related AE leading to treatment discontinuation*	3 (0.4)	1 (0.1)
SAE within 28 days of any vaccination	13 (1.6)	9 (1.1)
SAE through Day 336	32 (4.0)	21 (2.6)
Fatal SAE	0	0

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 31, pp. 98-99.
N = number of subjects with at least one documented dose; n (%) = number and percent of subjects reporting the adverse event at least once; AE = adverse event; MAAE = medically attended adverse event; NOCI = new-onset chronic illness (investigator-identified); SAE = serious adverse event
* Related was defined as very likely/certain, poss bly, or probably vaccine-related by the Investigator
** One subject in the Sci-B-Vac group is included here as discontinued due to an AE, who was listed as discontinued for "other" reason due to an "allergic reaction to vaccination."

Overall by subject, within 28 days of any dose, 46.4% and 48.0% of subjects in the Sci-B-Vac and Engerix-B groups, respectively, reported unsolicited AEs (serious and non-serious). The most frequently reported unsolicited AEs by PT were *Headache* (Sci-B-Vac 8.5%; Engerix-B 8.1%), *Upper respiratory tract infection* (Sci-B-Vac 6.3%; Engerix-B 6.4%), and *Fatigue* (Sci-B-Vac 4.1%; Engerix-B 4.9%). By PT, events that were reported potentially clinically significantly more frequently in the Sci-B-Vac group compared to the Engerix-B group included *Injection site pain* (Sci-B-Vac n=23, 2.9%; Engerix-B n=13, 1.6%) and *Gastroenteritis* (Sci-B-Vac n=10, 1.3%; Engerix-B n=4, 0.5%) with two additional subjects reporting *Gastroenteritis viral* in the Sci-B-Vac group. Notably, *Diarrhea* was reported in the Engerix-B group at approximately twice the rate of the Sci-B-Vac group (Sci-B-Vac n=10, 1.3%; Engerix-B n=21, 2.6%). The SOCs with the greatest proportions of subjects reporting unsolicited AEs were *Infections and infestations* (Sci-B-Vac 17.7%; Engerix-B 18.5%), *Musculoskeletal and connective tissue disorders* (Sci-B-Vac 12.5%; Engerix-B 13.1%), and *Nervous system disorders* (Sci-B-Vac 10.5%; Engerix B 11.4%).

Reviewer comment: *The incidence of unsolicited AEs in the 28 days following vaccination was similar in the two vaccine groups, overall and by PT.*

Within 28 days of any dose, there were four subjects in the Sci-B-Vac group and one in the Engerix-B group with AEs in the SMQ for *Angioedema*. Please see section 6.1.12.7 for a description of a subject who discontinued treatment due to tongue swelling and upper respiratory infection 13 days after dose 1. Regarding the other three events, one in the Sci-B-Vac group was serious but was ACE-inhibitor related and occurred 19 days post-vaccination. The other two events in the Sci-B-Vac group were non-serious AEs of urticaria. Please see the discussion of hypersensitivity events in section 8.4.4.

Grade 3 or greater, non-serious, unsolicited AEs within 28 days of any dose were reported in 42 subjects (5.3%) and 54 subjects (6.7%) in the Sci-B-Vac and Engerix-B groups, respectively. The most frequently reported non-serious, Grade 3 or greater, unsolicited AEs in the Sci-B-Vac group by PT were *Upper respiratory tract infection* (Sci-B-Vac n=5, 0.6%; Engerix-B n=5, 0.6%), *Headache* (Sci-B-Vac n=4, 0.5%; Engerix-B n=3, 0.4%), and *Back pain* (Sci-B-Vac n=3, 0.4%; Engerix-B n=4, 0.5%). The most frequently reported Grade 3 or greater, non-serious, unsolicited AEs in the Engerix-B group by PT were *Upper respiratory tract infection*, *Fatigue* (Sci-B-Vac n=2, 0.3%; Engerix-B n=5, 0.6%), *Back pain*, and *Myalgia* (Sci-B-Vac n=1, 0.1%; Engerix-B n=4, 0.5%). The SOCs in both groups with the most frequently reported Grade 3 or greater, non-serious, unsolicited AEs were *Infections and infestations* (Sci-B-Vac n=19, 2.4%; Engerix B n=22, 2.7%) and *Musculoskeletal and connective tissue disorders* (Sci-B-Vac n=10, 1.3%; Engerix-B n=13, 1.6%).

Two subjects reported Grade 4, non-serious AEs, one in each vaccine group. In the Sci-B-Vac group, a 69-year-old man reported a headache 25 days after dose 2, in the setting of an SAE of urosepsis, acute kidney injury, and thrombocytopenia. The headache was evaluated in the ER, potentially leading to the toxicity grade, and resolved 2 days later. This event was assessed by the investigator as unrelated to vaccination. The event in the Engerix-B group was *Herpes zoster ophthalmicus*.

Overall by subject, 122 (15.3%) subjects in the Sci-B-Vac group and 99 (12.2%) subjects in the Engerix-B group reported an unsolicited AE (serious or non-serious) within 28 days following any dose of study vaccine that was assessed as vaccine-related by the investigator. The most frequently reported unsolicited AEs assessed as related by PT were all PTs of solicited AEs; related *Injection site pain* was reported more frequently in the Sci-B-Vac group (21 subjects, 2.6% Sci-B-Vac and 13 subjects, 1.6% Engerix-B), while related *Fatigue*, *Headache*, and *Myalgia* were well balanced between vaccine groups. *Abdominal pain upper* assessed by investigators as related was reported in more subjects in the Sci-B-Vac group (4 subjects, 0.5%) compared to the Engerix-B group (0 subjects), as well as PTs in the higher level term (HLT) of *Upper respiratory tract infection* (Sci-B-Vac n=10, 1.3%; Engerix B n=5, 0.6%). Investigators assessed two non-serious AEs in the Sci-B-Vac group as "unclassifiable" for vaccine relatedness: a mild, non-medically attended AE of *Right lung wheezing* reported on the day of dose 2 of 29 days duration without other associated AEs, and a moderate, medically attended AE of *Dyspepsia* reported 26 days following dose 1.

Reviewer comment: *Slightly more subjects reported unsolicited AEs assessed by investigators as vaccine-related in the Sci-B-Vac group. Unsolicited related AEs of* Injection site reaction*,* Upper respiratory infection*, and* Abdominal pain upper *were*

reported more frequently in the Sci-B-Vac group, but at a low rate overall. The unclassifiable and vaccine-related events with onset beyond 28 days following vaccination do not change the risk-benefit of Sci-B-Vac.

Related, Grade 3 or greater, non-serious, solicited AEs within 28 days of vaccination were reported in 6 subjects (0.8%) in the Sci-B-Vac group and 8 subjects (1.0%) in the Engerix-B group. In the Sci-B-Vac group the PTs were *Blood pressure systolic increased*, *Upper respiratory tract infection*, *Headache*, *Gastroenteritis*, *Abdominal pain upper*, *Skin infection* (verbatim term "undefined infection in face").

Reviewer comment: *Overall, by nature and severity unsolicited AEs were reported at similar rates in each vaccine group.*

Medically attended adverse events

MAAEs were collected from the first dose to Day 336. This section discusses medically attended unsolicited AEs. Please see the discussion of solicited AEs that were medically attended above.

MAAEs within 28 days of vaccination were reported in 120 (15.1%) subjects in the Sci-B-Vac group and 149 (18.4%) subjects in the Engerix-B group. The most frequently reported MAAEs within 28 days of vaccination in both groups by PT were *Urinary tract infection* (Sci-B-Vac n=10, 1.3%; Engerix-B n=11, 1.4%), *Upper respiratory tract infection* (Sci-B-Vac n=9, 1.1%; Engerix-B n=5, 0.6%), *Sinusitis* (Sci-B-Vac n=5, 0.6%; Engerix-B n=8, 1.0%), and *Bronchitis* (Sci-B-Vac n=5, 0.6%; Engerix B n=5, 0.6%). Grade 3 or greater, non-serious MAAEs within 28 days of vaccination were reported in 23 subjects (2.9%) in the Sci-B-Vac group and 37 subjects (4.6%) in the Engerix-B group. *Urinary tract infection*, *Upper respiratory tract infection*, and *Bronchitis* were the only Grade 3, non-serious, MAAE PTs in the Sci-B-Vac group that were reported in more than one subject; each PT was reported in two subjects each in the Sci-B-Vac group and a similar number of subjects in the Engerix-B group.

From Day 1 to 336, medically attended AEs were reported in 202 (25.4%) subjects in the Sci-B-Vac group and 231 (28.5%) subjects in the Engerix-B group. The most common unsolicited medically attended events in the Sci-B-Vac group were *Urinary tract infection* (Sci-B-Vac n=17 (2.1%); Engerix-B n=17, 2.1%), *Upper respiratory tract infection* (Sci-B-Vac n=10, 1.3%; Engerix-B n=7, 0.9%), *Sinusitis* (Sci-B-Vac n=9, 1.1%; Engerix-B n=14, 1.7%), and *Bronchitis* (Sci-B-Vac n=8, 1.0%; Engerix-B n=6, 0.7%). From Day 1 to 336, Grade 3 or greater, non-serious, MAAEs were reported in 40 subjects (5.0%) in the Sci-B-Vac group and 60 subjects (7.4%) in the Engerix-B group.

MAAEs assessed by investigators as vaccine-related were reported by 8 subjects (1.0%) in the Sci-B-Vac group and 6 (0.7%) subjects in the Engerix-B group. PTs for the related MAAEs in the Sci-B-Vac group were *Swollen tongue* and *Upper respiratory tract infection* in one subject (see section 6.1.12.7) and *Atrial fibrillation*, *Gastroenteritis viral (SAE, see section 6.1.12.4)*, *Muscular weakness*, *Pruritus*, *Rosacea*, *Skin infection* (undefined infection in face, noted above), and *Urinary tract infection* in one subject each. PTs for the related MAAEs in the Engerix-B group were *Myalgia* and *Polymyalgia rheumatica (PMR)* in one subject (see section 6.1.12.7) and *Arthralgia*, *Influenza*, *Injection site pain*, *Rash papular*, and *Subcutaneous abscess* in one subject each.

New-onset chronic illnesses
NOCIs were collected by the investigator from vaccination to Day 336. In addition, the MM flagged AEs as NOCIs based on the CDC listing of chronic diseases.

Investigator-determined NOCIs were reported in 26 subjects (3.3%) in the Sci-B-Vac group and 30 subjects (3.7%) in the Engerix-B group. The MM considered that NOCIs were reported in 13 subjects (1.6%) in the Sci-B-Vac group and 14 subjects (1.7%) in the Engerix-B group. The assessments of the NOCIs agreed in 11 subjects in the Sci-B-Vac group and 12 subjects in the Engerix-B group. The MM identified an NOCI in four subjects who were not identified by investigators: *Anti-transglutaminase antibody increased* in one subject in the Sci-B-Vac group, *Hypothyroidism* in one subject in the Engerix-B group, and *Cerebrovascular accident* in one subject in each group.

When considering NOCIs that either the investigator or the MM identified, the most frequently reported PT in the Sci-B-Vac group was type 2 diabetes reported in 3 Sci-B-Vac recipients and 0 Engerix-B recipients. Events reported in 2 subjects in the Sci-B-Vac group and 0 Engerix-B subjects were *Congestive heart failure* (see section 6.1.12.4) and *Cataracts*. The most frequently reported PTs in the Engerix-B groups were *Hypertension* (2 subjects in the Sci-B-Vac group and 6 subjects in the Engerix-B group), *Hypothyroidism* (0 subjects in the Sci-B-Vac group and 5 subjects in the Engerix-B group), and *Hypercholesterolemia* (0 subjects in the Sci-B-Vac group and 3 subjects in the Engerix-B group).

When considering NOCIs that either the investigator or the MM identified, events assessed as vaccine-related by the Investigator were reported in 2 subjects in each group: *Headache* and *Injection site pain* in the Sci-B-Vac group and *Hypertension* and *PMR* in the Engerix-B group.

Reviewer comment: *Both NOCIs in the Sci-B-Vac group were mild reactogenicity events that resolved within 1-2 days duration; the Applicant believes they were entered as NOCIs in error.*

Brief narratives of select NOCIs that are potentially immune-mediated are presented here:

- Rheumatoid arthritis (severe) was diagnosed 14 days after dose 3 of Sci-B-Vac in a 73-year-old woman with medical history of ongoing generalized osteoarthritis, osteoporosis, hypertension, hyperlipidemia, type 2 diabetes, sleep apnea, multiple drug hypersensitivities and seasonal allergies. She began treatment with hydroxychloroquine the same day as the AE start date.

  Reviewer comment: *It is likely that this subject began having symptoms prior to 14 days post-dose 3, but the timing with regard to doses 1 and 2 is not reported. It also appears from the medical history that this subject had long-standing arthritic and musculoskeletal conditions. Also of note, the subject reported a quinine allergy at enrollment, suggesting she had prior exposure to quinine, though the indication of previous use is unknown and no hypersensitivity is reported with hydroxychloroquine. Based on the available information, this event represents a new-onset immune-mediated event post-vaccination. Of note, NOCIs of PMR were reported in two subjects in the Engerix-B group (7 days post-dose 2 in a 71-year-old woman, assessed as possibly related, and 128 days post-dose 3 in a 68-year-old woman).*

- *Anti-transglutaminase antibody increased* (mild) was reported 118 days post-dose 2 of Sci-B-Vac in a 43-year-old woman with no medical history, indicating a potentially new-onset of celiac disease. This was identified as an NOCI by the MM, not the investigator.

- Cold urticaria (moderate and non-serious) was reported to have occurred between 5 and 35 days post-dose 3 of Sci-B-Vac (exact day was not reported) in a 38-year-old woman with a past medical history of hydronephrosis of pregnancy. No other recent infections were reported. Cetirizine is reported as being started approximately 3 months later and the event was ongoing at the end of the study approximately 6 months later.

  Reviewer comment: *Cold urticaria has been associated with various infections, including hepatitis, (Barranco Sanz, 1987) although a causal relationship is unknown and it is not included in the MedDRA SMQ for* Immune-mediated/ autoimmune disorders*. In this case, for which no additional information was provided by the Applicant, Sci-B-Vac is temporally associated with new onset of cold urticaria.*

  Additional potentially immune-mediated NOCIs include hypothyroidism (reported in 0 subjects in the Sci-B-Vac and 5 subjects in the Engerix-B group), chronic gastritis (reported in 0 subjects in the Sci-B-Vac and one subject in the Engerix-B group), and gout (reported in one subject in each group).

6.1.12.3 Deaths

There were no deaths reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

All SAEs were monitored through Day 336, approximately 6 months following the third dose. A summary of SAEs occurring up to 30 days following any dose and throughout the study period is below.

Table 21. Treatment-Emergent SAEs Within 28 Days of Any Dose of Study Vaccine and Day 1 Through Day 336, Sci-B-Vac-001, Safety Set

Adverse Event	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
SAEs within 28 days following any dose	13 (1.6)	9 (1.1)
SAEs Day 1 through Day 336	32 (4.0)	21 (2.6)
Fatal SAE Day 1 through Day 336	0	0
Related SAE within 28 days following and dose	1 (0.1)	0
Related SAE Day 1 through Day 336	1 (0.1)	0

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 51, pp. 129-130 and Sci-B-Vac-001 Tables, Figures, Listings, Tables 14.3.1.3.1, pp. 9365-9403, and 14.3.1.3.2, pp. 9404-9743.
N = number of subjects receiving the specified dose; n (%) = number and percent of subjects reporting the adverse event at least once

Up to 28 days following any dose of study vaccine, 13 subjects (1.6%) in the Sci-B-Vac arm and 9 subjects (1.1%) in the Engerix-B group reported SAEs. No SAEs in this period were reported in more than one subject in a vaccine group. The most commonly reported SAEs were *Cholelithiasis* and *Osteoarthritis*, each reported by one subject in

each group. The most commonly reported SOCs in the Sci-B-Vac group were *Infections and infestations* (n=3, PTs of *Urosepsis*, *Influenza*, and *Gastroenteritis viral*), *Injury, poisoning and procedural complications* (n=2, PTs of *Joint dislocation* and *Tendon rupture*) and *Nervous system disorders* (n=2, PTs of *Syncope* and *Peroneal nerve palsy*). No more than one SAE was reported in each SOC by subjects in the Engerix-B group. One subject reported angioedema in the Sci-B-Vac group 18 days after the third dose, attributed to an angiotensin converting enzyme-inhibitor, as noted above.

Reviewer comment: *Within 28 days of any dose, the percentage of subjects that reported SAEs was similar between groups and low overall.*

One subject (0.1%) in the Sci-B-Vac group reported an SAE within 28 days of any dose of study vaccine that was assessed by the investigator as related. No subjects in the Engerix-B group reported an SAE assessed as related.

- A 54-year-old man with hypertension, diabetes, obesity, sleep apnea, anxiety, depression, neck/knee/back pain and gastroesophageal reflux disease received two doses of Sci-B-Vac and reported nausea, vomiting and diarrhea 5 days after dose 2. He was hospitalized for worsening diarrhea 7 days after the onset of symptoms. He underwent a work-up, which revealed extensive diverticulosis, and was diagnosed with "probable viral gastroenteritis." He was discharged from the hospital 5 days later and the event was considered resolved after a total of 23 days. He discontinued from vaccination and from the study due to the event. The investigator assessed the event as probably related. The Applicant considered this event not related.

Reviewer comment: *This event of gastroenteritis has a temporal relationship with vaccination and a prolonged, atypical course. There was one additional non-serious, Grade 3 AE of gastroenteritis assessed by the investigator as possibly related reported the day after dose 1 of Sci-B-Vac. However, solicited AEs of nausea/vomiting and diarrhea were not clinically significantly increased in the Sci-B-Vac group compared to the Engerix-B group. While unsolicited AEs of gastroenteritis (Sci-B-Vac n=10, 1.3%; Engerix-B n=4, 0.5%) and gastroenteritis viral (Sci-B-Vac n=3, 0.4%; Engerix B n=0) within 28 days of vaccination were reported more frequently in the Sci-B-Vac group, unsolicited AEs of diarrhea (Sci-B-Vac n=10, 1.3%; Engerix-B n=21, 2.6%) and vomiting (Sci-B-Vac n=1, 0.1%; Engerix-B n=3, 0.4%) were reported more frequently in the Engerix-B group. Aside from the timing, there is no other evidence suggesting a relationship to vaccination.*

Review of the narratives of other SAEs do not suggest causal relationship to vaccination.

During the study period, from Day 1 through Day 336, SAEs were reported in 32 subjects (4.0%) in the Sci-B-Vac group and 21 subjects (2.6%) in the Engerix-B group. One SAE PT was reported in more than one subject in the Sci-B-Vac group – *Congestive cardiac failure* (Sci-B-Vac n=2; Engerix-B n=0). Two SAE PTs were reported in more than one subject in the Engerix-B group – *Atrial fibrillation* (Sci-B-Vac n=1; Engerix-B n=2) and *Colon cancer* (Sci-B-Vac n=0; Engerix B n=2). The SOCs with the greatest proportions of subjects reporting SAEs were *Infections and infestations* (Sci-B-Vac n=7, 0.9%; Engerix-B n=3, 0.4%), *Neoplasms, benign, malignant, and unspecified* (Sci-B-Vac n=4, 0.5%; Engerix-B n=5, 0.6%), *Cardiac disorders* (Sci-B-Vac n=5, 0.6%; Engerix-B n=3, 0.4%), *Injury, poisoning, and procedural complications* (Sci-B-Vac n=4, 0.5%; Engerix-B n=3, 0.4%), *Nervous system disorders* (Sci-B-Vac n=4, 0.5%; Engerix-

B n=1, 0.1%), and *Gastrointestinal disorders* (Sci-B-Vac n=2, 0.3%; Engerix-B n=3, 0.4%). Other than the SAE of viral gastroenteritis described above, no SAEs were assessed by investigators as related.

Reviewer comment: *There was a small numerical imbalance in overall SAEs reported during the study; the nature of the SAEs was varied and generally reflected events anticipated based on the age and medical status of the study population (subjects with stable chronic diseases).*

In a reviewer-generated analysis by narrow SMQ, the greatest between-group differences (more than one subject difference) in SAEs were in the SMQs for *Embolic and Thrombotic Events* (Sci-B-Vac n=3; Engerix-B n=1), and *Cardiac failure* (Sci-B-Vac n=2; Engerix-B n=0). The three embolic or thrombotic events in the Sci-B-Vac group were *Cerebral infarct* (35 days post-dose 2 in a 53-year-old man), *Myocardial infarction* (136 days post-dose 3 in a 51-year-old man), and *Cerebral vascular accident* (ischemic event occurring 136 days post-dose 3 in a 67-year-old woman). In the Engerix-B group, the SAE in the SMQ for *Embolic and thrombotic events* was *Cerebrovascular accident* (44 days post-dose 2 in a 62-year-old man). Regarding MAAEs, the SMQ for *Embolic and Thrombotic Events* during the entire study identified 5 subjects (0.6%) in the Sci-B-Vac group and 3 subjects (0.4%) in the Engerix-B group, which includes the above SAEs. One subject, a 65-year-old man, in the Sci-B-Vac group reported a non-serious, medically attended deep vein thrombosis (DVT) of moderate severity on the day of dose 3, assessed as unrelated to vaccination by the investigator. The other non-serious MAAEs in the *Embolic and Thrombotic Events* SMQ in both vaccine groups were reported more than 100 days post-vaccination.

Reviewer comment: *All subjects with SAEs in the SMQ for* Embolic and thrombotic events *had baseline medical histories indicating risk for cardiovascular events. Review of the narratives did not suggest a relationship to vaccination. The non-serious DVT that occurred on the day of vaccination is temporally too close in onset to vaccination to suggest causal immune-mediated relationship. There is not a clear increase risk of embolic and thrombotic events following Sci-B-Vac compared to Engerix-B.*

With regard to the two SAEs in the SMQ for *Cardiac failure*, both with PTs of *Cardiac failure congestive* reported in the Sci-B-Vac group, brief narratives are presented below:

- A 54-year-old woman with asthma, anxiety and headaches, who was a current smoker and was receiving fluoxetine, received three doses of Sci-B-Vac. Vital signs collected during the study suggested elevated Stage 2 systolic hypertension. She presented with 3 weeks of cough and shortness of breath, beginning approximately 26 days after the third dose and was diagnosed with acute congestive heart failure 47 days after the third dose of Sci-B-Vac. Chest X-ray showed cardiomegaly and bilateral pulmonary edema. Echocardiography revealed acute systolic heart failure exacerbation with diastolic dysfunction, moderate right ventricular systolic function, and severely elevated right ventricular systolic pressure. Cardiac catheterization revealed no coronary artery disease or obstruction. She was treated with carvedilol, furosemide, and sacubitril/valsartan and the event resolved with sequelae. The investigator assessed the event as unrelated to vaccination.
- A 72-year-old woman with hyperlipidemia, hypertension and type 2 diabetes was diagnosed with an unsolicited AE of moderate *Atrial fibrillation* 35 days post-dose 1 of Sci-B-Vac. Following this, she presented with shortness of breath and was

hospitalized and diagnosed with decompensated congestive heart failure 100 days after the second dose of Sci-B-Vac. Following treatment and discharge, she was admitted 10 days later with an SAE of *Nodal arrhythmia* and non-serious AEs of severe acute (on chronic) renal failure and mild elevation in serum potassium. Atrial fibrillation and congestive heart failure were ongoing at study conclusion; the other events resolved. She received dose 3 without additional SAEs reported. These SAEs and AEs were assessed as unrelated or unlikely related by the investigator.

Reviewer comment: *No cause was identified for the first subject with non-ischemic congestive heart failure; however, her work-up, revealing cardiomegaly, suggests long-standing disease. The second subject had risk factors for cardiovascular disease and onset was greater than 3 months from vaccination. There were no additional events of congestive heart failure identified in Sci-B-Vac-002, although that study enrolled younger subjects. One event of sudden cardiac death in a subject with pre-existing hypertrophic heart disease and prior cardiac surgery who received Sci-B-Vac was reported (see section 6.2.12.3) in Sci-B-Vac-002. Other imbalances in cardiovascular events were not noted in the safety data.*

6.1.12.5 Adverse Events of Special Interest (AESI)

Not applicable.

6.1.12.6 Clinical Test Results

Subjects at select sites in Canada and at the site in Belgium were enrolled in the clinical laboratory sub-study, which assessed hematology and biochemistry parameters pre-vaccination, and 7 days following each dose (Days 7, 35 and 175). In total 193 subjects of 1,607 subjects in the Safety Set (12.0%) were included in the clinical laboratory subset (SSA1, 96 subjects in the Sci-B-Vac and 97 subjects in the Engerix-B group).

Hematology evaluations included hemoglobin, platelet count, white blood cell (WBC) count with differential, mean cell hemoglobin, mean cell hemoglobin concentration, and mean corpuscular volume. No clinically significant changes from pre-vaccination to each post-dose time point were observed based on mean values of each of the hematologic parameters.

No Grade 4 hematologic abnormalities were reported. The following are summaries of hematologic changes from pre-vaccination (normal to Grade 2) to Grade 3 post-vaccination in the SSA1:

- Sci-B-Vac
    - One subject had a decrease in hemoglobin from Grade 2 pre-vaccination (10.2 g/dL) to Grade 3 (9.1 g/dL) at Day 35. At Day 175, hemoglobin was normal (13.0 g/dL). No AE was reported associated with this shift, but the subject began taking ferrous fumarate at the time of the Grade 3 abnormality.
    - One subject had a decrease in lymphocyte count from normal pre-vaccination (1710 cells/mm^3) to Grade 3 (310 cells/mm^3) at Day 175. The subject's other WBC parameters at Day 175 were normal. The subject's lymphocyte counts at other time points were normal. No AEs were reported at the time of the abnormal lymphocyte count.

- Engerix-B
    - One subject had a decrease in lymphocyte count from normal pre-vaccination (1920 cells/mm^3) to Grade 3 (320 cells/mm^3) at Day 35. Lymphocyte count was normal at Day 175. Other WBC parameters were within normal limits. The subject reported mild to moderate dizziness and headaches prior to her second dose and a moderate toothache following dose 2, 5 days prior to the lab draw and returning 4 days after the lab draw for 11 days.
    - One subject had a decrease in hemoglobin from normal pre-vaccination (15.8 g/dL) to Grade 1 (13.2 g/dL) at Day 175. This qualified as a Grade 3 decrease due to the change of 2.6 g/dL. Gingivitis and toothache are reported around the time of the subject's third dose, but no AEs to explain the hemoglobin decrease.

Based on all unsolicited AEs reported in the datasets on all subjects, no subjects in the Sci-B-Vac group and two subjects in the Engerix-B group had treatment-emergent hematologic abnormalities considered to be clinically significant by investigators.

Reviewer comment: *No clinically significant laboratory abnormalities that are likely to be vaccine related were identified.*

Biochemistry evaluations included blood urea nitrogen (BUN), serum creatinine, alkaline phosphatase (AP), ALT, aspartate transaminase (AST), total and conjugated bilirubin and gamma-glutamyl-transferase (GGT). No clinically significant changes from pre-vaccination to each post-dose time point were observed based on mean values of each of the biochemistry parameters.

The following are summaries of biochemistry changes from pre-vaccination (normal to Grade 2) to Grade 3 post-vaccination in the SSA1:

- Sci-B-Vac
    - One subject had an increase in BUN from Grade 1 (8.3 mmol/L) at Day 1 to Grade 3 (12.8 mmol/L) at Day 7, returning to the subject's pre-vaccination level at Day 35. No creatinine elevation was seen and no unsolicited AEs were reported.
    - One subject had an increase in BUN from Grade 1 (8.4 mmol/L) at screening and Grade 2 (10.8 mmol/L) at Day 1 to Grade 3 (11.2 mmol/L) at Day 7, returning to Grade 2 (9.6 mmol/L) at Day 35 and normal at Day 175 (7.0 mmol/L). No creatinine abnormalities are reported. Mild hypotension was reported on Day 29, the day of the second dose, which is reported as ending on the day of the third dose.
    - One subject had an increase in BUN from Grade 1 (8.2 mmol/L) at screening and normal (7.6 mmol/L) at Day 1 to Grade 2 (10.0 and 10.2 mmol/L) at Days 7 and 35, and Grade 3 (12.8 mmol/L) at Day 175. The subject's creatinine was above the upper limit of normal, but did not reach a Grade 1 abnormality. No unsolicited AEs are reported.
- Engerix-B
    - One subject in the Engerix-B group had Grade 3 elevations in ALT and Grade 4 elevations in AST at Day 7 and 35 associated with cholelithiasis requiring urgent cholecystectomy.
    - One subject had an increase in BUN from normal (4.6 mmol/L) at screening and Grade 1 at Day 1 (7.8 mmol/L) to Grade 3 (14.2 mmol/L) at

Day 7. At Day 7, creatinine increased over pre-vaccination, but remained normal (89 mcmol/L). No associated unsolicited AEs were reported.

Including the above listed shifts in BUN, in the CSR, the Applicant reported a number of shifts in BUN from normal, Grade 1 or 2 to Grade 3 at Day 7, 35 or 175 laboratory assessments, representing 12 Sci-B-Vac recipients (12.5%) and 7 Engerix-B recipients (7.2%). As the reviewer noted that a majority of Grade 3 abnormalities were reported at one site and many of these values were within the reference range for that site, the Applicant was queried about these inconsistencies. In 125737/0.31, the Applicant clarified that blood urea, instead of BUN had been assessed at this site, but a correction factor had not been applied in the analysis. None of these BUN elevations were accompanied with elevations of other markers of renal function, such as serum creatinine, nor were they assessed as clinically significant by study investigators and reported as AEs.

Reviewer comment: *The number of subjects with BUN abnormalities was incorrectly reported. In those subjects with shifts to Grade 3, the lack of AEs reported in association with the BUN shifts suggests there are no clinically significant BUN abnormalities.*

Based on all unsolicited AEs reported in the datasets on all subjects, one subject in the Sci-B-Vac group and 0 subjects in the Engerix-B group had treatment-emergent biochemistry abnormalities considered to be clinically significant by investigators. This 72-year-old woman was diagnosed with *Congestive heart failure* during the study and had a non-serious Grade 1 increased blood potassium in the setting of an SAE of *Nodal arrhythmia* and non-serious AE of acute renal failure, assessed as unrelated to vaccination (see section 6.1.12.4).

Reviewer comment: *No clinically significant biochemical laboratory abnormalities that are likely to be vaccine related were identified.*

Vital signs: The Applicant monitored vital signs pre- and 30 minutes post-vaccination ("Other" solicited AEs) and graded abnormalities according to FDA guidance on toxicity grading for vaccine trials (FDA, 2007). Please see section 6.1.12.2 for an assessment of fever. The number and proportion of subjects with post-vaccination vital signs out of normal range is shown in the table below.

Table 22. Solicited "Other" Adverse Events Assessed 30 Minutes Following Any Dose of Sci-B-Vac or Engerix-B, Sci-B-Vac-001, Safety Set

Solicited "Other" Adverse Event	Sci-B-Vac N=796 n (%)	Engerix-B N=811 n (%)
Hypotension (systolic)	3 (0.4)	1 (0.1)
Hypertension (systolic)	226 (28.4)	248 (30.6)
Hypertension (diastolic)	144 (18.1)	138 (17.0)
Bradycardia (beats/min)	92 (11.6)	74 (9.1)
Tachycardia (beats/min)	4 (0.5)	4 (0.5)
Respiratory Rate, increased (breaths/min)	199 (25.0)	202 (24.9)

Source: 125737/0.0, Sci-B-Vac-001 CSR, Table 44, p. 115.
N = number of subjects receiving the specified dose; n (%) = number and percent of subjects reporting the adverse event at least once

One subject in the Sci-B-Vac group had a medically attended "other" solicited AE; a 48-year-old woman with severe diastolic hypertension after dose 3, increased from Grade 2 pre-vaccination.

Reviewer comment: *Similar proportions of subjects reported vital sign abnormalities post-vaccination in both treatment groups. The Applicant presented proportions of subjects with post-vaccination vital sign abnormalities by severity, age group, and dose (not shown). No clinically significant between-group differences were identified.*

6.1.12.7 Dropouts and/or Discontinuations

In the Sci-B-Vac and Engerix-B groups, 4.8% and 3.2% of subjects did not receive all three doses. AEs leading to treatment discontinuation were reported in 6 (0.8%) Sci-B-Vac recipients and 5 (0.6%) Engerix-B recipients. Three subjects in the Sci-B-Vac group and one subject in the Engerix-B group reported AEs assessed as related by investigators leading to treatment discontinuation:

- SAE of *Gastroenteritis* (see section 6.1.12.4) reported 5 days after dose 2 of Sci-B-Vac.
- Non-serious, mild AEs of *Asthenopia* (verbatim term "feeling of heaviness in both eyes") and *Hypoesthesia oral* (verbatim term "feeling numb from the mouth"), assessed as very likely/certainly related, beginning the day of dose 1 of Sci-B-Vac in a 49-year-old man. These events resolved the same day without treatment and were not medically attended. The subject also reported a moderate headache on the day of vaccination, treated with ibuprofen and resolving the next day (see also section 8.4.4).
- Non-serious moderate AEs of *Tongue swelling* (probably related) and *Upper respiratory infection* (very likely or certainly related) 13 days after dose 1 of Sci-B-Vac in a 68-year-old man. *Tongue swelling* resolved after 11 days.
- Non-serious severe AEs of *Myalgia* and *PMR*, both assessed as possibly related, beginning 6 days after dose 2 of Engerix-B in a 71-year-old woman.

Reviewer comment: *The subject with* Asthenopia *and* Hypoesthesia oral *was classified as having an "other" reason for study discontinuation of allergic reaction to vaccine. This event is included in the reviewer's count of treatment discontinuation due to adverse events, but not the Applicant's.*

Unrelated SAEs leading to treatment discontinuation were reported in one subject who received Sci-B-Vac and two subjects who received Engerix-B:

- *Invasive ductal breast carcinoma* in one subject who received Sci-B-Vac
- *Cholelithiasis* and *Colon cancer* in one subject each who received Engerix-B

Non-serious unrelated AEs that led to discontinuation included:

- Severe worsening of hypotension on the day of dose 1 of Sci-B-Vac resolving after 29 days duration in a 76-year-old woman with hypotension pre-vaccination. The subject's blood pressure decreased from 84/53 (Grade 2) to 76/49 (Grade 3), requiring discontinuation from treatment per protocol, despite the subject remaining asymptomatic.
- Moderate DVT 101 days after dose 2 of Sci-B-Vac in a 67-year-old man with hypertension and obesity.
- Depression (verbatim term "worsening of depression") and verbatim term "adenocarcinoma metastasis of liver" in two subjects in the Engerix-B group

Although listed as a discontinuation due to a forbidden medication, one 66-year-old woman with a medical history of "suspected ankylosing spondylitis" (verbatim term), fibromyalgia, and back pain for 9 years, and osteoarthritis for 7 years prior to study enrollment withdrew due to starting sulfasalazine for a non-serious MAAE of severe worsening back pain, which began 20 days following dose 1 of Sci-B-Vac and was assessed as unrelated.

Reviewer comment: *Most subjects completed treatment. Few subjects discontinued treatment due to an adverse event and three subjects who received Sci-B-Vac discontinued due to an adverse event considered at least possibly related by investigators. In the reviewer's judgement it is unclear that the gastroenteritis and the tongue swelling are related to vaccination. The third event, asthenopia and oral hypoesthesia, appears to be related to vaccination given the timing of the event. However, these reactions were mild and resolved quickly without medical assessment or intervention. Please see the discussion of allergic reactions in section 8.4.4. The subject who discontinued due to initiation of sulfasalazine appears to have had a worsening of an inflammatory arthropathy following Sci-B-Vac administration, although the Applicant did not have additional details on diagnosis or prior history of sulfasalazine use in this subject (125737.025).*

In the Sci-B-Vac and Engerix-B groups, 5.0% and 5.2% of subjects, respectively, withdrew before completing the study (before Day 336). AEs (serious and non-serious) leading to study withdrawal were reported in 0.1% of Sci-B-Vac recipients (1 subject) and 0.4% (3 subjects) of Engerix-B recipients.

- The subject who received Sci-B-Vac and reported the SAE of *Gastroenteritis*, which was assessed as related, discontinued the study, as well as treatment due to the AE.
- The subject who received Engerix-B and reported *Myalgia* and *PMR*, both of which were assessed as related, discontinued the study, as well as treatment due to the AE.
- The two subjects who received Engerix-B and reported *Depression* and "adenocarcinoma metastasis of liver," which were both assessed as unrelated, discontinued the study, as well as vaccination, due to the AEs.

Two additional subjects in the Engerix group discontinued vaccination due to SAEs and withdrew from the study for other reasons – *Colon cancer* and *Cholelithiasis*. The subject who started sulfasalazine for worsening back pain/ankylosing spondylitis following Sci-B-Vac was also discontinued from the study, as well as vaccination, due to "other" – forbidden medication.

Reviewer comment: *Most subjects completed the study. One subject in each group discontinued the study due to an adverse event assessed as related. As 95% of subjects completed the study, safety data collection is not likely to be impacted by study discontinuations.*

6.1.13 Study Summary and Conclusions

Sci-B-Vac-001 was a Phase 3, multi-center, multi-national, double-blind, randomized, active-controlled trial to evaluate the immunogenicity and safety of Sci-B-Vac. A total of 1,607 HBV vaccine-naïve adults 18 YOA and older were enrolled and vaccinated with at least one dose of a three-dose series of Sci-B-Vac or Engerix-B. Enrollment was

targeted to ensure 80% of subjects were ≥45 YOA (and 40% ≥65 YOA). Two co-primary objectives were defined by the Applicant: (1) demonstration of non-inferiority of Sci-B-Vac to Engerix-B, as measured by SPR at Day 196, 4 weeks after the third dose, in all adults ≥18 YOA, and (2) demonstration of statistical superiority of Sci-B-Vac to Engerix-B at Day 196 in adults ≥45 YOA.

For the first co-primary endpoint of non-inferiority in adults ≥18 YOA, the SPR was 91.4% (95% CI: 89.1, 93.3) in the Sci-B-Vac group and 76.5% (95% CI: 73.22, 79.53) in the Engerix-B group, resulting in a difference in SPR (Sci-B-Vac−Engerix-B) of 14.9%. The LB of the 95% CI of the difference in SPR was 11.2%, greater than the preset non-inferiority margin of −5%. Therefore, non-inferiority of Sci-B-Vac compared with Engerix-B 4 weeks after the third dose in subjects ≥18 YOA was demonstrated. For the second co-primary endpoint of superiority in adults ≥45 YOA, the SPR at Day 196 was 89.4% (95% CI: 86.8, 91.7) in the Sci-B-Vac group and 73.1% (95% CI: 69.4, 76.5) in the Engerix-B group, resulting in a difference in SPR (Sci-B-Vac−Engerix-B) of 16.4%. The LB of the 95% CI of the difference in SPR was 12.2%, which was greater than the Applicant's preset margin of >0%. The study met both of its co-primary endpoints. Subgroup analyses suggest the immunogenicity results were generally consistent with the analyses in the total study population.

IS pain and tenderness were the most commonly reported solicited local symptoms after Sci-B-Vac administration, reported in a majority of subjects and at greater frequencies than in the Engerix-B group. Myalgia, headache, and fatigue were the most commonly reported solicited systemic symptoms after Sci-B-Vac administration. Across all age groups, myalgia was the only solicited AE reported more frequently in the Sci-B-Vac group compared to the Engerix-B group. Fever was uncommon. In general, local and systemic solicited symptoms tended to be reported at the highest frequencies in the Sci-B-Vac group following the first dose. Most local and systemic solicited AEs were reported at decreasing frequencies with increasing age. In general, unsolicited AEs were reported at similar frequencies between groups and between-group differences were not judged to be clinically significant.

6.2 Trial #2

Sci-B-Vac-002: 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 the manufacturing equivalence, in terms of immunogenicity, of three independent consecutive lots of Sci-B-Vac 4 weeks after the third dose

Secondary objectives

- To demonstrate that the SPR 4 weeks after completion of the three-dose regimen of Sci-B-Vac is non-inferior to a three-dose regimen of Engerix-B
- To assess the safety and reactogenicity of Sci-B-Vac compared to Engerix-B

Exploratory objectives

- To assess the GMC of anti-HBs in serum after two doses, just before receiving the third dose (Day 168), and 24 weeks after the third dose (Day 336) of Sci-B-Vac or Engerix-B

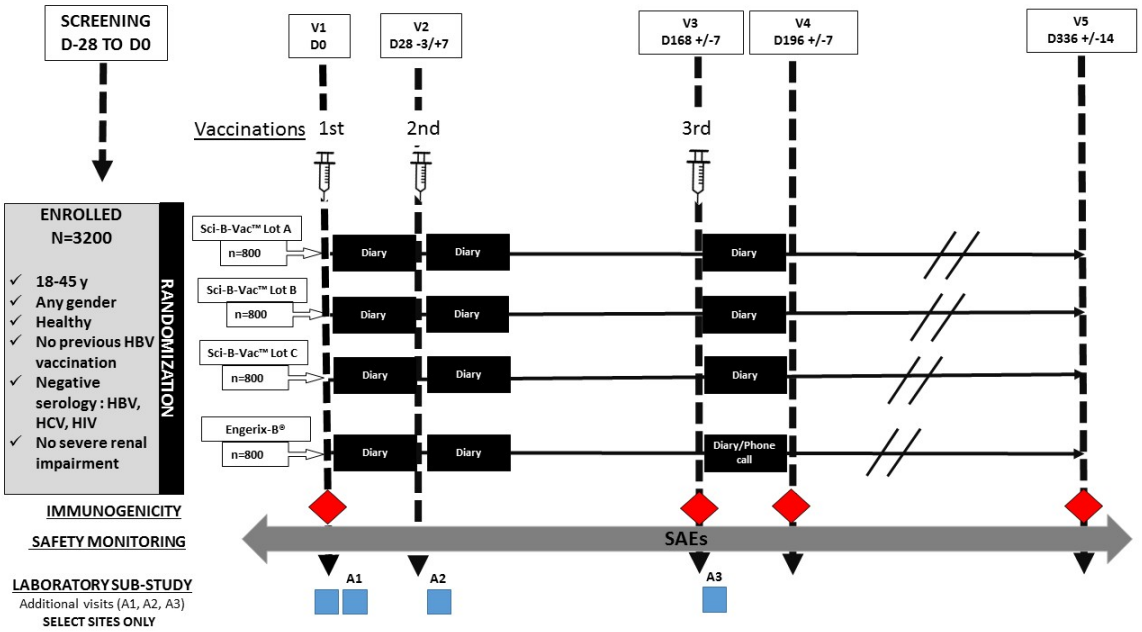
- To assess the SPR after two doses, just before receiving the third dose (Day 168), and 24 weeks after the third dose of Sci-B-Vac or Engerix-B
- To assess the proportion of subjects achieving anti-HBs titers ≥100 mIU/mL in serum, as a measure of an especially robust immune response, just before (Day 168) and 4 weeks after the third dose (Day 196) of Sci-B-Vac or Engerix-B, and on Day 336
- To assess the rate of non-response 4 weeks after the third dose (Day 196) of Sci-B-Vac or Engerix-B
- To assess SPR, GMC, and rate of non-response in subgroups of interest (for example, subjects with BMI >30 kg/m^2), 4 weeks after receiving the third dose (Day 196) of Sci-B-Vac or Engerix-B

6.2.2 Design Overview

This study was a double-blind, four-arm, randomized, active-controlled study to demonstrate the manufacturing equivalence of three lots of Sci-B-Vac and to assess the immunogenicity and safety of a three-dose series of Sci-B-Vac compared to a three-dose series of Engerix-B in adults 18 through 45 YOA. Subjects were randomized 1:1:1:1 to receive either one of three lots of Sci-B-Vac (Lots A, B, or C) or Engerix-B, administered IM on Days 0, 28, and 168.

The study included a 4-week screening period to determine subject eligibility. Enrolled subjects visited the study sites for a total of 5 visits (screening and V1 through V5) and were followed for 48 weeks after the first dose, 24 weeks after receiving the third dose. There was a safety follow-up 7 days after each dose conducted by telephone to inquire about local and systemic reactions. There was an additional telephone contact on Day 56, 4 weeks after the second dose to assess the subject's status. Based on these follow-up assessments, subjects may have been asked to come for a supplemental visit for clinical assessment if warranted. Safety evaluations included additional visits (A1-A3) to perform laboratory testing (blood chemistry and CBC) on Days 0 (V1), 7, 35, and 175 in a subset of subjects (at least 10% of the total number of subjects) enrolled at select study sites. Immunogenicity (measurement of anti-HBs) was assessed at Days 0, 168, 196, and 336. A schematic of the study design is provided below.

Figure 1. Schematic of Study Design. Sci-B-Vac-002



Source: 125737/0.0, Sci-B-Vac-002 CSR, Figure 2, p. 24.
A = additional visit; D = day; HBV = hepatitis B virus; HCV = hepatitis C virus; n = number of subjects planned to be enrolled; SAE = serious adverse event; V = visit; y = years

6.2.3 Population

Key inclusion criteria

- Individuals 18 through 45 YOA
- Able and willing to provide consent
- Healthy, as determined by a physical examination and laboratory tests
- If a women of childbearing potential, agreed to use an acceptable method of contraception during the screening period and through the end of study participation

Key exclusion criteria

- Previous vaccination with any HBV vaccine
- Current or past hepatitis B infection (anti-HBc, anti-HBs, HBsAg performed at screening)
- Known hepatitis C infection unless treated and cured; Known HIV
- Renal impairment with GFR <60 mL/min/1.73 m^2 at screening
- BMI ≥35 kg/m^2
- Diabetes mellitus, type 1 or 2, or HbA1C ≥6.5%) at screening
- Uncontrolled hypertension (average SBP ≥150 mmHg or average DBP ≥95 mmHg based on the last three measurements)
- Any laboratory test abnormality ≥ Grade 1 severity and clinically significant as per the investigator, or ≥ Grade 3 severity, regardless of investigator's clinical assessment
- History of cancer requiring chemotherapy or radiation within 5 years
- History of allergic or anaphylactic reaction to any vaccine component of either vaccine
- Treatment with immunosuppressant within 30 days

- Known history of immunological function impairment, including autoimmune disease, primary or secondary immunodeficiency
- Pregnant or breastfeeding
- Live attenuated vaccine within 4 weeks or inactivated vaccine within 2 weeks prior to enrollment
- Receipt of blood products or immunoglobulin within 90 days or granulocyte-macrophage colony stimulating factor or erythropoietin within 30 days of enrollment, or likely to receive during the study

Reviewer comment: *Because the primary objective was to assess lot-to-lot consistency, the study population was limited to young (≤45 YOA), healthy subjects, a population that has been shown to have better responses to HBV vaccination.*

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study products were:

- Sci-B-Vac: supplied as 1 mL single-dose vials. Each 1 mL single-dose vial contained 10 mcg of hepatitis B surface antigens (pre-S1, pre-S2, and S) adsorbed on 0.5 mg aluminum hydroxide. The product also contained sodium chloride, potassium chloride, disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate anhydrous and water for injection. Three independent consecutive lots of Sci-B-Vac were used, Lot numbers: B1291V1 (Lot A), B1331V1 (Lot B), and B1301V1 (Lot C).
- Engerix-B: supplied as 1 mL vials. Each 1 mL single-dose vial contained 20 mcg of HBsAg adsorbed on 0.5 mg aluminum hydroxide. Lot numbers: B39CM and T9AK3.

6.2.5 Directions for Use

Either Sci-B-Vac or Engerix-B was administered to subjects as a three-dose series in a volume of 1 mL by IM injection in the deltoid on Days 0, 28, and 168. The first dose was given in the deltoid muscle of the nondominant arm and subsequent doses were alternated between the dominant and nondominant arms.

6.2.6 Sites and Centers

The study was conducted at 37 study centers including 5 in Canada, 17 in Europe, and 15 in the United States.

Table 23. Number of Subjects by Center, Country, and Region Sci-B-Vac-002, Safety Set

Country	Site No.	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot A N=705 n (%)	Pooled Sci-B-Vac N=2127 n (%)	Engerix-B N=712 n (%)
Canada	**All sites**	**31 (4.4)**	**29 (4.1)**	**30 (4.3)**	**90 (4.2)**	**31 (4.4)**
Canada	106	8 (1.1)	7 (1.0)	7 (1.0)	22 (1.0)	8 (1.1)
Canada	107	7 (1.0)	7 (1.0)	7 (1.0)	21 (1.0)	8 (1.1)
Canada	108	7 (1.0	7 (1.0)	8 (1.1)	22 (1.0)	7 (1.0)
Canada	111	9 (1.3	8 (1.1)	8 (1.1)	25 (1.2)	8 (1.1)

Country	Site No.	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot A N=705 n (%)	Pooled Sci-B-Vac N=2127 n (%)	Engerix-B N=712 n (%)
United States	**All sites**	**191 (26.9)**	**186 (26.3)**	**185 (26.2)**	**562 (26.5)**	**188 (26.4)**
US	200	14 (2.0)	14 (2.0)	14 (2.0)	42 (2.0)	13 (1.8)
US	202	11 (1.5)	11 (1.6)	11 (1.6)	33 (1.6)	11 (1.5)
US	203	5 (0.7)	5 (0.7)	4 (0.6)	14 (0.7)	5 (0.7)
US	204	14 (2.0)	14 (2.0)	14 (2.0)	42 (2.0)	15 (2.1)
US	205	22 (3.1)	21 (3.0)	20 (2.8)	63 (3.0)	21 (2.9)
US	206	11 (1.5)	11 (1.6)	11 (1.6)	33 (1.6)	11 (1.5)
US	207	25 (3.5)	25 (3.5)	24 (3.4)	74 (3.5)	25 (3.5)
US	208	13 (1.8)	12 (1.7)	13 (1.8)	38 (1.8)	12 (1.7)
US	209	14 (2.0)	12 (1.7)	13 (1.8)	39 (1.8)	13 (1.8)
US	210	3 (0.4)	3 (0.4)	3 (0.4)	9 (0.4)	3 (0.4)
US	211	24 (3.4)	24 (3.4)	23 (3.3)	71 (3.3)	24 (3.4)
US	212	6 (0.8)	5 (0.7)	5 (0.7)	16 (0.8)	6 (0.8)
US	213	2 (0.3)	3 (0.4)	3 (0.4)	8 (0.4)	2 (0.3)
US	214	15 (2.1)	15 (2.1)	15 (2.1)	45 (2.1)	15 (2.1)
US	215	12 (1.7)	11 (1.6)	12 (1.7)	35 (1.6)	12 (1.7)
Europe	**All sites**	**489 (68.8)**	**493 (69.6)**	**490 (69.5)**	**1472 (69.3)**	**493 (69.2)**
Belgium	300	8 (1.1)	8 (1.1)	8 (1.1)	24 (1.1)	9 (1.3)
Germany	400	3 (0.4)	2 (0.3)	2 (0.3)	7 (0.3)	2 (0.3)
Finland	601	47 (6.6)	49 (6.9)	48 (6.8)	144 (6.8)	47 (6.6)
Finland	602	49 (6.9)	48 (6.8)	49 (7.0)	146 (6.9)	49 (6.9)
Finland	603	39 (5.5)	38 (5.4)	38 (5.4)	115 (5.4)	39 (5.5)
Finland	604	44 (6.2)	44 (6.2)	44 (6.2)	132 (6.2)	43 (6.0)
Finland	605	59 (8.3)	59 (8.3)	60 (8.5)	178 (8.4)	59 (8.3)
Finland	606	44 (6.2)	44 (6.2)	43 (6.1)	131 (6.2)	45 (6.3)
Finland	607	38 (5.3)	40 (5.6)	38 (5.4)	116 (5.5)	38 (5.3)
Finland	608	49 (6.9)	50 (7.1)	49 (7.0)	148 (7.0)	52 (7.3)
Finland	609	29 (4.1)	30 (4.2)	30 (4.3)	89 (4.2)	30 (4.2)
Finland	610	33 (4.6)	31 (4.4)	32 (4.5)	96 (4.5)	32 (4.5)
United Kingdom	500	16 (2.3)	17 (2.4)	16 (2.3)	49 (2.3)	16 (2.2)
United Kingdom	501	17 (2.4)	19 (2.7)	18 (2.6)	54 (2.5)	17 (2.4)
United Kingdom	502	6 (0.8)	5 (0.7)	6 (0.9)	17 (0.8)	6 (0.8)
United Kingdom	503	8 (1.1)	9 (1.3)	9 (1.3)	26 (1.2)	9 (1.3)

Source: Adapted from 125373/0.0 Sci-B-Vac-002 Section 14 Tables, Figures, Listings, Table 14.1.2.3, p. 34.; and 125737/0.25, Table 2, pp. 4-5.
Note: Site is the initial site of subject randomization.
N = number of subjects in the total group; n (%) = number and percent of subjects enrolled at the clinical site.

Reviewer comment: *Two sites (one in Canada and one in Germany) did not enroll any subjects. A majority of subjects enrolled were from Europe (69.3%) and more specifically from Finland (61.0%). However, the United States was well represented, enrolling 26.4% of subjects.*

6.2.7 Surveillance/Monitoring

Study oversight
Study center monitoring was conducted by (b) (4)

An independent DMC, comprising five members, was established to monitor subject safety. Members of the DMC were responsible for reviewing safety reports and data and, in the event a stopping rule was triggered, determining whether the clinical trial was to be stopped or required modification in order to proceed safely.

Safety assessments
Collection of solicited AEs (local, systemic, and other), unsolicited AEs (including SAEs, MAAEs, and NOCIs), one-week post-vaccination safety phone call, stopping rules, concomitant medications, and pregnancy were the same as in Sci-B-Vac-001 except that the 28-day post-dose 2 visit was conducted by telephone. Please see section 6.1.7 for details.

Safety assessments – laboratory assessments
All subjects had hematology, biochemistry, urinalysis, and serology (HBV, hepatitis C virus, and HIV), assessed at screening to determine study eligibility. At select sites, subjects were asked to participate in a clinical laboratory sub-study to include at least 10% of the total number of subjects enrolled in the trial. Subjects enrolled at these sites attended three additional visits (A1, A2, A3) and provided four additional blood samples to assess hematology and biochemistry parameters pre-vaccination (V1), and 7 days following each dose. Laboratory abnormalities were assessed via the same processes as in Sci-B-Vac-001 (see section 6.1.7).

Immunogenicity assessments
Immunogenicity was assessed by measurement of anti-HBs levels at baseline (Day 0), and at Study Days 168, 196, and 336. A validated VITROS anti-HBs quantitative assay measured anti-HBs levels in serum.

6.2.8 Endpoints and Criteria for Study Success

Primary endpoint
GMC of anti-HBs in serum 4 weeks after the third dose of Sci-B-Vac, on Study Day 196, as the basis for assessing lot-to-lot consistency.

Secondary endpoints

- (Immunogenicity) SPR 4 weeks after the third dose of Sci-B-Vac or Engerix-B, on Study Day 196.

  Seroprotection was defined as anti-HBs levels of ≥10 mIU/mL in serum and SPR was the percentage of subjects achieving seroprotection.

  Success criterion for the secondary objective:
  - The lower bound of the two-sided 95% confidence interval (CI) of the difference between the SPR in the Sci-B-Vac arm minus the SPR in the Engerix-B arm, achieved 4 weeks after receiving the third dose, was >-5%

- (Safety) Number (%) of subject-reported solicited AEs (on the day of vaccination and during the next 6 days), unsolicited AEs (on the day of vaccination and during the next 27 days), and SAEs, medically significant events, or NOCIs through Study Day 336)
- (Safety) Number (%) of subjects with abnormal vital signs and physical examination findings compared with baseline
- (Safety) Number (%) of subjects with abnormal clinical laboratory parameters from baseline assessments on Study Days 7, 35, and 175, one week after each dose of either Sci-B-Vac or Engerix-B

Exploratory endpoints

- GMC and SPR of anti-HBs in serum on Days 168 (after 2 doses, just before receiving the third dose) and 336 (24 weeks after the third dose) for Sci-B-Vac or Engerix-B groups
- SPR, GMC, and rate of non-response in subgroups of interest (e.g., subjects with a BMI >30 kg/m^2), 4 weeks after receiving the third dose of Sci-B-Vac or Engerix-B

Reviewer comment: *Additional exploratory objectives assessed the proportion of subjects with anti-HBs ≥100 mIU/mL post-vaccination and rate of non-response, but these assessments will not contribute to the risk-benefit assessment and so are not discussed below. As anamnestic responses and protection from HBV disease have been demonstrated in young healthy subjects who achieve anti-HBs ≥10 mIU/mL following vaccination, the clinical benefit of anti-HBs ≥100 mIU/mL in this population is not established and is not discussed further.*

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size

The sample size for this study was determined by the lot-to-lot consistency objective. A total of 800 subjects in each of the three Sci-B-Vac lots would provide at least 90% power to ensure that the 95% CI for each pairwise comparison (GMC ratios of anti-HBs in the three lots) in normalized log10 (GMC) has a lower bound that is >-0.176 and an upper bound that is <0.176 if the true SD is ≤0.9; this corresponds to the true GMC ratio falling between [0.67, 1.5]. With an active comparator arm of Engerix-B of equal size (n=800), the total sample size of the study was 3,200. In addition, with a sample size of 3,200, there would be >90% power to demonstrate the non-inferiority of Sci-B-Vac compared to Engerix-B, assuming 10% of the subjects are non-evaluable, a two-sided 5% significance level, and a non-inferiority margin of -5%.

In October 2018, the Applicant closed enrollment early for non-safety related reasons after 2,838 subjects were randomized to the study due to a slow rate of enrollment. With approximately 700 subjects in each of the lot groups and comparator group, the sample size would provide >80% power to evaluate both the primary objective of lot-to-lot consistency and the secondary objective of non-inferiority.

Reviewer comment: *In a Type C Meeting held on October 3, 2019, CBER agreed with the Applicant's proposal to submit a BLA with a total safety database of approximately 2,923 subjects having received at least one dose of Sci-B-Vac assuming no safety signals were observed. The Applicant did not consult with the CBER prior to closing enrollment for the study.*

Missing and implausible data
See section 6.1.9.

Analysis of efficacy/immunogenicity
Primary objective: The primary analysis to determine the lot-to-lot consistency of three independent consecutive lots of Sci-B-Vac was conducted on PPS1, with sensitivity analyses on the PPS2. Adjusted estimates of GMCs and their associated 95% CIs were each determined using an ANCOVA model with a factor for lot and a covariate for the log-transformed pre-vaccination (baseline) titer. The ratios in GMCs between each vaccine lot group and their associated two-sided 95% CIs were calculated. If the upper and lower bound of the two-sided 95% CI of the GMC of anti-HBs ratios 4 weeks after the third dose for all three pairwise comparisons were within [0.67, 1.5] in the PPS1 the lot-to-lot consistency (manufacturing equivalence) was demonstrated.

Secondary objective: If lot-to-lot consistency was demonstrated, then the data from the three lots of Sci-B-Vac were to be combined to assess non-inferiority of Sci-B-Vac compared to Engerix-B as determined by the SPR at Day 196, 4 weeks after completion of the three-dose regimens. The analysis was based on the PPS2. The difference in SPRs (Sci-B-Vac−Engerix-B) and two-sided 95% CIs, was calculated using the Miettinen and Nurminen method. If the lower bound of the 95% CI was >−5%, Sci-B-Vac was determined to be non-inferior to Engerix-B.

Analysis of safety
The Safety Set (defined as all subjects who received at least one dose of vaccine, analyzed as treated) was the population used for most safety analyses. Clinical safety laboratory assessments were based on the SSA Set. Safety analyses were descriptive and were provided by time of occurrence relative to the last vaccination as pre-specified in the study objectives. For unsolicited AEs, the verbatim terms reported by investigators in the eCRFs were mapped to PTs using MedDRA version 20.1.

Reviewer comment: *Please see the statistical review for further details about the statistical methods used for the immunogenicity and safety analyses.*

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Please see section 6.1.10.1 for the definitions of the All Enrolled Set, Safety Set, ITT, FAS, and the Sub-Study Analysis Set (identical to the Clinical Laboratory Sub-Study Analysis Set [SSA1] in Sci-B-Vac-001). The following are the definitions of the two per protocol sets:

- Per Protocol Set 1 (PPS1): All subjects in the FAS who received all three doses, had evaluable serum immunogenicity samples at baseline and at the timepoint of interest, were seronegative at baseline, and had no major protocol deviations leading to exclusion as identified prior to unblinding.
- Per Protocol Set 2 (PPS2): All subjects in PPS1, excluding those who attended study visits outside of the following windows:
    - V3 (Day 168): +/- 28 days
    - V4 (Day 196): -7/+14 days

  Subjects in PPS1 and PPS2 were analyzed as randomized and subjects who received the wrong vaccine were excluded. If a subject received a vaccine from

the wrong kit number, but the same vaccine as the one the subject was randomized to, the subject was not excluded. If a subject was unblinded during the study, except due to a SUSAR, he or she could be excluded based on Applicant's decision with respect to any potential bias that may be introduced.

Reviewer comment: *The statistical analysis plan for Sci-B-Vac-002 initially proposed to assess the primary objective on both the PPS1 and PPS2 and to declare manufacturing equivalence if success criteria were met using either analysis set. CBER advised the Applicant to pre-specify one analysis population for the primary analysis or propose an appropriate multiplicity adjustment to avoid inflation of familywise type I error rate. The Applicant defined the PPS1 as the primary analysis population prior to database lock and unblinding. They justify this choice based on 1) the results of Sci-B-Vac-001 study, which demonstrated no significant impact of out-of-window study visits on the SPR observed after the third dose (similarity of the Sci-B-Vac SPR for the FAS and the PPS analysis populations), 2) the expectation that the younger, healthier and more homogeneous population enrolled to Sci-B-Vac-002 would be expected to have more stable antibody concentrations over time, which would not be sensitive to out-of-window assessments, and 3) variability between lots as a result of out-of-window visits would not be expected to affect vaccine efficacy. They selected the PPS2 for the secondary comparative objective to avoid any perceived or real bias that could favor Sci-B-Vac, if Sci-B-Vac was less affected by out-of-window assessments than Engerix-B. The different analysis sets for the primary and secondary objectives were pre-specified by the Applicant and found to be acceptable.*

6.2.10.1.1 Demographics
The summary of demographic characteristics of the Safety Set is below.

Table 24. Demographic Characteristics, Sci-B-Vac-002, Safety Set

Characteristic	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Sci-B-Vac Pooled N=2124 n (%)	Engerix-B N=712 n (%)	Total N=2836 n (%)
Gender						
Male	303 (42.6)	313 (44.2)	291 (41.3)	907 (42.7)	291 (40.9)	1198 (42.2)
Female	408 (57.4)	395 (55.8)	414 (58.7)	1217 (57.3)	421 (59.1)	1638 (57.8)
Race						
White	650 (91.4)	641 (90.5)	650 (92.2)	1941 (91.4)	654 (91.9)	2595 (91.5)
Asian	9 (1.3)	15 (2.1)	13 (1.8)	37 (1.7)	9 (1.3)	46 (1.6)
Black or African American	46 (6.5)	43 (6.1)	34 (4.8)	123 (5.8)	38 (5.3)	161 (5.7)
American Indian or Alaska Native	2 (0.3)	1 (0.1)	3 (0.4)	6 (0.3)	2 (0.3)	8 (0.3)
Other	4 (0.6)	8 (1.1)	5 (0.7)	17 (0.8)	9 (1.3)	26 (0.9)
Ethnicity						
Hispanic or Latino	64 (9.0)	70 (9.9)	61 (8.7)	195 (9.2)	74 (10.4)	269 (9.5)
Non-Hispanic or Latino	643 (90.4)	638 (90.1)	643 (91.2)	1924 (90.6)	636 (89.3)	2560 (90.3)
Not collected per local guidelines	4 (0.6)	0	1 (0.1)	5 (0.2)	2 (0.3)	7 (0.2)

Characteristic	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Sci-B-Vac Pooled N=2124 n (%)	Engerix-B N=712 n (%)	Total N=2836 n (%)
Age at informed consent (years)						
Mean (SD)	33.8 (8.0)	32.9 (8.0)	33.9 (7.9)	33.5 (8.0)	33.4 (8.1)	33.5 (8.0)
Median	36.0	34.0	36.0	35.0	35.0	35.0
Min, Max	18, 45	18, 45	18, 45	18, 45	18, 45	18, 45
Geographic location						
United States	191 (26.9)	186 (26.3)	185 (26.2)	562 (26.5)	188 (26.4)	750 (26.4)
Europe	489 (68.8)	493 (69.6)	490 (69.5)	1472 (69.3)	493 (69.2)	1965 (69.3)
Canada	31 (4.4)	29 (4.1)	30 (4.3)	90 (4.2)	31 (4.4)	121 (4.3)

Source: 125737/0.0, Sci-B-Vac-002 CSR, Table 17, pp. 67-69.
Note: Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects in the total group; n (%) = number and percent of subjects with the demographic characteristic; max = maximum; min = minimum; SD = standard deviation

Majorities of subjects were female (57.8%), non-Hispanic or Latino (90.3%) and White (91.5%). The mean (SD) age of study subjects was 33.5 (8.0) years.

Reviewer comment: *No clinically significant between-group differences were identified by demographic characteristics. As in Sci-B-Vac-001, few Asians were enrolled.*

The Applicant presented demographics by vaccine group in the other analysis populations. No clinically significant between-group differences were noted in the ITT, FAS, PPS1, or the PPS2. In the clinical laboratory SSA Set, 92.4% of subjects were from the United States with the remainder from Canada. More subjects in this subset were Black or African American (21.6%) and Hispanic or Latino (22.1%) compared to the Safety Set (5.7% and 9.5%, respectively), though clinically significant between-group differences in race or ethnicity were not observed in this population. In the SSA Set, there was more variability in gender between groups. Subjects receiving Lot A were majority male (56.4%), while subjects who received Lot B, Lot C and Engerix-B were minority male (49.0%, 42.9%, and 47.9%). This has the potential to affect safety laboratory comparisons between lots of Sci-B-Vac but would not be expected to affect comparison of pooled Sci-B-Vac (49.5% male) to Engerix-B (47.9% male).

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The summary of medical and behavioral characteristics of the Safety Set is below.

Table 25. Medical and Behavioral Characteristics, Sci-B-Vac-002, Safety Set

Characteristic	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Sci-B-Vac Pooled N=2124 n (%)	Engerix-B N=712 n (%)	Total N=2836 n (%)
BMI (kg/m^2)						
Mean (SD)	25.92 (4.22)	25.75 (4.00)	25.97 (4.17)	25.88 (4.12)	25.69 (4.10)	25.83 (4.11)
Median	25.68	25.37	25.73	25.55	24.97	25.43
Min, Max	16.1, 34.9	16.3, 34.9	13.9, 34.9	13.9, 34.9	16.3, 34.9	13.9, 34.9
BMI category						
≤30 kg/m^2	576 (81.0)	591 (83.5)	570 (80.9)	1737 (81.8)	595 (83.6)	2332 (82.2)
>30 kg/m^2	135 (19.0)	117 (16.5)	135 (19.1)	387 (18.2)	117 (16.4)	504 (17.8)

Characteristic	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Sci-B-Vac Pooled N=2124 n (%)	Engerix-B N=712 n (%)	Total N=2836 n (%)
Smoking status/tobacco use*						
Current smoker/tobacco user	139 (19.5)	142 (20.1)	125 (17.7)	406 (19.1)	136 (19.1)	542 (19.1)
Former smoker/tobacco user	137 (19.3)	131 (18.5)	136 (19.3)	404 (19.0)	141 (19.8)	545 (19.2)
Non-smoker/non-tobacco user	435 (61.2)	435 (61.4)	443 (62.8)	1313 (61.8)	435 (61.1)	1748 (61.6)
Average daily alcohol consumption						
0-1 drink/day	673 (94.7)	660 (93.2)	659 (93.5)	1992 (93.8)	653 (91.7)	2645 (93.3)
2-3 drinks/day	32 (4.5)	45 (6.4)	43 (6.1)	120 (5.6)	54 (7.6)	174 (6.1)
≥4 drinks/day	6 (0.8)	3 (0.4)	3 (0.4)	12 (0.6)	5 (0.7)	17 (0.6)

Source: 125737/0.0, Sci-B-Vac-002 CSR, Table 17, pp. 67-69.
Note: Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects in the total group; n (%) = number and percent of subjects with the medical or behavioral characteristic; BMI = body mass index; max = maximum; min = minimum; SD = standard deviation
* One subject in Sci-B-Vac Lot C did not have information in the datasets for smoking status. This subject is included in the denominator.

Majorities of subjects were not obese (82.2%), non-smokers (61.6%), and reported 0-1 alcoholic drinks per day (93.3%). Subjects median BMI was 25.4 kg/m^2.

Reviewer comment: *There were no clinically significant between-group differences.*

The Applicant presented medical characteristics by vaccine group in the other analysis populations. No clinically significant between-group differences were noted in the ITT, FAS, PPS1, or the PPS2. Compared to the Safety Set, more subjects in the SSA Set were obese (30.0% vs. 17.8%). In the SSA Set, Sci-B-Vac Lot groups varied with respect to percentage of obese subjects (Lot B 25.5%; Lot C 34.7%) and smoking status (Lot B 60.2% non-smokers; Lot C 69.4% non-smokers). The pooled Sci-B-Vac arm was similar to the Engerix-B arm in percentage of obese subjects and percentage of non-smokers. The impact of these differences on safety laboratory values is not known.

The Applicant presented an analysis of medical history by vaccine group. The percentage of subjects with any medical history reported was similar between groups (pooled Sci-B-Vac: 68.0%, range 66.2% in Lot C to 68.9% in Lots A and B; Engerix-B: 70.1%). The most commonly reported medical history findings by SOC were Immune system disorders (27.6%); all of the reported PTs in this SOC were related to allergies. The most common medical history findings by PT were seasonal allergy (19.4%), depression (7.8%), and migraine (7.0%).

Reviewer comment: *No clinically significant between-group differences in medical history were identified.*

6.2.10.1.3 Subject Disposition
An overview of the analysis populations used for evaluation of safety and immunogenicity endpoints is provided below.

Table 26. Analysis Populations, Sci-B-Vac-002, Intent-to-Treat

Analysis Set	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=709 n (%)	Sci-B-Vac Lot C N=706 n (%)	Pooled Sci-B-Vac N=2126 n (%)	Engerix-B N=712 n (%)	Total N=4452 n (%)
All Enrolled Set[a]						4452
Intent-to-Treat (ITT)[b]	711	709	706	2126	712	2838
Safety Set[c]	711 (100.0)	708 (99.9)	705 (99.9)	2124 (99.9)	712 (100.0)	2836 (99.9)
Full Analysis Set (FAS)[d]	650 (91.4)	661 (93.2)	656 (92.9)	1967 (92.5)	673 (94.5)	2640 (93.0)
Per Protocol Set 1 (PPS1)[e]	620 (87.2)	622 (87.7)	627 (88.8)	1869 (87.9)	642 (90.2)	2511 (88.5)
Per Protocol Set 2 (PPS2)[f]	590 (83.0)	591 (83.4)	597 (84.6)	1778 (83.6)	603 (84.7)	2381 (83.9)
Clinical Laboratory Sub-Study Analysis (SSA) Set[g]	101 (14.2)	98 (13.8)	98 (13.9)	297 (14.0)	96 (13.5)	393 (13.8)

Source: Adapted from 125737/0.0, Sci-B-Vac-002 CSR, Table 14, p. 61.
Note: Percentages are based on the ITT population. Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects in the total group; n (%) = number and percent of subjects in the analysis population
a All Enrolled Set included all screened subjects who provided informed consent and demographic and/or baseline screening assessments.
b ITT included all subjects in the All Enrolled Set who were randomized.
c Safety Set included all subjects in the All Enrolled Set who received at least one dose of vaccine.
d FAS included all subjects who received at least one dose of vaccine and provided at least one evaluable serum immunogenicity sample both at and after baseline.
e PPS1 included all subjects in the FAS who received all three doses, had an evaluable serum immunogenicity sample at baseline and at the time point of interest, were seronegative at baseline, and had no major protocol violations leading to exclusion.
f PPS2 included all subjects in PPS1 excluding subjects who attended visits outside of the following windows: V3/Day 168 (±28 days) and V4/Day 196 (-7/+14 days).
g Clinical Laboratory Sub-Study Analysis (SSA) Set included all subjects in the All Enrolled Set who received at least one dose of vaccine and participated in the clinical laboratory sub-study.

The total number of subjects screened and included in the All Enrolled Set was 4,452 subjects. The ITT population, which included all randomized subjects, comprised 2,126 subjects in the pooled Sci-B-Vac arms and 712 subjects in the Engerix-B arm. Of 2,838 randomized subjects, 2,836 received at least one dose and thus, were included in the Safety Set. Two subjects randomized to Sci-B-Vac (one to Lot B and one to Lot C) were not included in the Safety Set as they were never vaccinated.

Of 2,836 randomized and vaccinated subjects, 2,640 (93.1%) subjects were included in the FAS (92.6% in the pooled Sci-B-Vac arms and 94.5% in the Engerix-B arm). Of 2,836 randomized and vaccinated subjects, 2,511 (88.5%) subjects were included in the PPS1 for analysis of the primary endpoint of lot-to-lot consistency (88.0% of the pooled Sci-B-Vac arms) and 2,381 (84.0%) were included in the PPS2 for analysis of the secondary immunogenicity endpoint of non-inferiority of Sci-B-Vac to Engerix-B (83.7% in the pooled Sci-B-Vac arms and 84.7% in the Engerix-B arm).

Reviewer comment: *The proportions of subjects in the Safety Set and ITT that were included in the FAS, PPS1, and PPS2 for the analyses of efficacy were comparable between treatment groups. Although 11.5 and 16.1% of subjects were not included in the PPS1 and PPS2, respectively, the Applicant presented sensitivity analyses based on other analysis populations (see section 6.2.11).*

Exposure

The table below shows the total number of vaccine doses received.

Table 27. Number and Percentage of Subjects by Total Number of Vaccine Doses Received, Sci-B-Vac-002, Safety Set

Total Number of Doses Received	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Pooled Sci-B-Vac N=2124 n (%)	Engerix-B N=712 n (%)
1 dose	21 (3.0)	13 (1.8)	19 (2.7)	53 (2.5)	10 (1.4)
2 doses	39 (5.5)	33 (4.7)	32 (4.5)	104 (4.9)	31 (4.4)
3 doses	651 (91.6)	662 (93.5)	654 (92.8)	1967 (92.6)	671 (94.2)

Source: 125737/0.0, Sci-B-Vac-002 CSR, Table 33, p. 90.
Note: Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects in the total group; n (%) = number and percent of subjects who received the specified total number of doses

Most subjects, 92.6% of the pooled Sci-B-Vac arms and 94.2% of the Engerix-B arm, received three doses of vaccine.

Reviewer comment: *Less than 10% of subjects in each vaccine group discontinued treatment. Slightly more subjects in the Sci-B-Vac groups (6.5%-8.5%) discontinued treatment compared to the Engerix-B group (5.8%).*

The table below presents the reasons for discontinuation of treatment.

Table 28. Discontinuations from Treatment and Reason, Sci-B-Vac-002, Safety Set

Discontinuations and reasons	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Pooled Sci-B-Vac N=2124 n (%)	Engerix-B N=712 n (%)
Discontinued from treatment	60 (8.4)	46 (6.5)	51 (7.2)	157 (7.4)	41 (5.8)
Reason for discontinuation of treatment					
SAE	2 (0.3)	0	0	2 (0.1)	1 (0.1)
Non-serious AE	3 (0.4)	4 (0.6)	2 (0.3)	9 (0.4)	1 (0.1)
Pregnancy	3 (0.4)	3 (0.4)	5 (0.7)	11 (0.5)	2 (0.3)
Other	52 (7.3)	39 (5.5)	44 (6.2)	135 (6.4)	36 (5.1)

Source: Adapted from 125737/0.0, Sci-B-Vac-002 CSR, Table 15, p. 63-64.
Note: Percentages are based on the number of subjects vaccinated. Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects in the total group; n (%) = number and percent of subjects who discontinued treatment for the specified reason; SAE = serious adverse event; AE = adverse event

Of the subjects who did not complete treatment, most in all groups discontinued for "Other" reasons. "Other" reasons included lost to follow-up or withdrawal of consent.

Reviewer comment: *More subjects in the Sci-B-Vac arm discontinued treatment for "Other" reasons. A reviewer analysis determined that 3.7% (Lot B) – 4.8% (Lot A) of Sci-B-Vac groups and 2.8% of subjects in the Engerix-B group were lost to follow-up and 1.3% (Lot B) – 2.1% (Lot A) of Sci-B-Vac groups and 1.3% of subjects in the Engerix-B group withdrew consent. The remainder of the "other" reasons were reviewed and did not suggest vaccine-related AEs.*

Protocol deviations

Of 2,836 subjects vaccinated, 33.2% had at least one protocol deviation during the study that was classified by the Applicant as major (33.2% in the Pooled Sci-B-Vac group and 33.1% in the Engerix-B group). The most common major protocol deviations were

related to procedures or tests not performed in accordance with the protocol (538 subjects, 19.0%), followed by out-of-window or missing visits (356 subjects, 12.6%). Major protocol deviations that led to exclusion from the PPS2, the population used for the comparative analysis, were reported in 193 subjects (9.1%) in the Sci-B-Vac group and 70 subjects (9.8%) in the Engerix-B group. These deviations do not include other reasons for exclusion from the PPS1 and 2 (for examples, subjects who did not receive three doses or were seropositive at baseline). The most commonly reported protocol deviations that resulted in exclusion from the PPS2 were out of window or missing visit (pooled Sci-B-Vac n=123, 5.8%; Engerix-B n=44, 6.2%) and vaccine administration errors (pooled Sci-B-Vac n=43, 2.0%; Engerix-B n=14, 2.0%), primarily administration of an incomplete dose.

Reviewer comment: *The Applicant classified most missing protocol-specified procedures (for example, missing diary card information or vital signs) as major protocol deviations thus resulting in a higher rate of major protocol deviations than would usually be expected. The Applicant did not include subjects who discontinued treatment in the major protocol deviations leading to exclusion from PPS1 and PPS2, though these subjects were not included in those analysis sets. Protocol deviations were reviewed, and different types of deviations were reported at similar frequencies in each vaccine group. Investigational product administration errors leading to PPS exclusion were more frequently reported in Sci-B-Vac-002 compared to Sci-B-Vac-001. A majority of these protocol deviations occurred at one of two sites and were due to remaining vaccine being found in a used vial. This error affected 11-15 subjects per group and would not be anticipated to have a significant effect on the evaluation of overall safety.*

Disposition

Of the 2,836 subjects in the Safety Set, 297 subjects withdrew prior to completing the study (pooled Sci-B-Vac n=228, 10.7%; Engerix-B n=69, 9.7%). The table below shows subject disposition in the ITT population.

Table 29. Number and Percentage of Subjects Discontinued from the Study and Reason, Sci-B-Vac-002, Intent-to-Treat

Disposition	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=709 n (%)	Sci-B-Vac Lot C N=706 n (%)	Sci-B-Vac Pooled N=2126 n (%)	Engerix-B N=712 n (%)
Safety Set	711 (100.0)	708 (99.9)	705 (99.9)	2124 (99.9)	712 (100.0)
Completed treatment	651 (91.6)	662 (93.4)	654 (92.6)	1967 (92.5)	671 (94.2)
Discontinued from treatment	60 (8.4)	47 (6.6)	52 (7.4)	159 (7.5)	41 (5.8)
Completed study	636 (89.5)	637 (89.8)	625 (88.5)	1898 (89.3)	643 (90.3)
Withdrew prior to completing the study	75 (10.5)	72 (10.2)	81 (11.5)	228 (10.7)	69 (9.7)
Reason for early study discontinuation					
SAE	2 (0.3)	0	0	2 (0.1)	0
Non-serious AE	2 (0.3)	3 (0.4)	1 (0.1)	6 (0.3)	1 (0.1)
Lost to follow-up	49 (6.9)	51 (7.2)	51 (7.2)	151 (7.1)	48 (6.7)
Consent withdrawal, not due to an AE	15 (2.1)	13 (1.8)	17 (2.4)	45 (2.1)	12 (1.7)
Pregnancy	3 (0.4)	2 (0.3)	6 (0.8)	11 (0.5)	1 (0.1)
Moved from the study area	3 (0.4)	1 (0.1)	3 (0.4)	7 (0.3)	5 (0.7)
Non-compliance with study procedures	0	1 (0.1)	1 (0.1)	2 (0.1)	0
Major protocol violation warranting study withdrawal per medical monitor	0	0	2 (0.3)	2 (0.1)	0

Disposition	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=709 n (%)	Sci-B-Vac Lot C N=706 n (%)	Sci-B-Vac Pooled N=2126 n (%)	Engerix-B N=712 n (%)
Request of regulatory agency, or Applicant or Principal Investigator	0	0	0	0	1 (0.1)
Investigator decided that withdrawal from the study was in the best interest of the subject	0	1 (0.1)	0	1 (0.0)	0
Any clinically significant change in subject's medical condition*	1 (0.1)	0	0	1 (0.0)	0
Other	0	0	0	0	1 (0.1)

Source: Adapted from 125737/0.0, Sci-B-Vac-002 CSR.
Note: Percentages are based on the number of subjects randomized. Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects in the total group; n (%) = number and percent of subjects with the specified study or treatment status or who discontinued the study for the specified reason; SAE = serious adverse event; AE = adverse event
* A 35-year-old woman with a history of chronic lumbar and left leg pain and atopy, discontinued the study for a change in medical condition; she reported four SAEs (hospitalizations) due to worsening left lower limb or back pain, the first beginning 67 days post-dose 2 of Sci-B-Vac (Lot A).

The most common reasons for early discontinuation from the study were lost to follow-up (pooled Sci-B-Vac 7.1%; Engerix-B 6.7%) and withdrawal of consent (pooled Sci-B-Vac 2.1%; Engerix-B 1.7%).

Reviewer comment: *Most (89.3%-90.3%) study subjects completed the study and thus were followed for approximately 6 months following the last dose. Slightly more subjects discontinued the study due to AEs (0.4% and 0.1%, respectively) and pregnancy (0.5% and 0.1%, respectively) in the pooled Sci-B-Vac group compared to the Engerix-B group; but the numbers of subjects discontinuing for these reasons was low overall (see sections 6.2.12.7 and 9.1.1, respectively, for additional details). Otherwise, a similar percentage of subjects withdrew prior to completing the study in all treatment groups.*

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The analysis of the primary objective of demonstrating manufacturing consistency of three independent lots of Sci-B-Vac, as measured by GMC of anti-HBs, was based on the PPS1. The tables below show the results of this analysis.

Table 30. Geometric Mean Concentration of anti-HBs at Day 196, Sci-B-Vac-002, Per Protocol Set 1

Statistic	Sci-B-Vac Lot A N=620	Sci-B-Vac Lot B N=622	Sci-B-Vac Lot C N=627
Number of subjects evaluated	611	610	619
Mean	5883.9	4824.1	5505.9
Median	12200.0	10700.0	12000.0
Min, Max	2.1, 20000.0	2.1, 20000.0	2.1, 20000.0
Mean adjusted GMC (SE)	5882.3 (1.07)	4821.7 (1.07)	5569.9 (1.07)
95% CI	5112.4, 6768.0	4190.1, 5548.4	4844.6, 6403.7

Source: 125737/0.0, Sci-B-Vac-002 CSR, Table 21, pp. 74.
N = total number of subjects in the group; anti-HBs = hepatitis B surface ant body; GMC = geometric mean concentration; CI = confidence interval; max = maximum; min = minimum; SD = standard deviation; SE = standard error
Adjusted GMC and corresponding 95% CI were analyzed using ANCOVA with a factor for vaccine lot group, and a covariate for the log-transformed pre-vaccination (baseline) titer.

Table 31. Lot-to-Lot Consistency Comparisons of the Adjusted Geometric Mean Concentration Ratios, Sci-B-Vac-002, Per Protocol Set 1

Comparison	GMC Ratio (95% CI)
Lot A vs. Lot B	0.82 (0.67, 1.00)
Lot A vs. Lot C	0.95 (0.78, 1.15)
Lot B vs. Lot C	1.16 (0.95, 1.41)

Source: 125737/0.0, Sci-B-Vac-002 CSR, Table 21, pp. 74.
Note: The mean and SD are based on log10-transformed data, then transformed back to anti-HBs titer. Adjusted GMC, GMC ratio, and corresponding 95% CI were analyzed using ANCOVA with a factor for vaccine lot group, and a covariate for the log-transformed pre-vaccination (baseline) titer.
GMC = geometric mean concentration; CI = confidence interval

At Day 196, the mean adjusted GMCs of anti-HBs were 5,882.3 mIU/mL, 4,821.7 mIU/mL, and 5,569.9 mIU/mL across Lots A, B, and C of Sci-B-Vac, respectively. The adjusted GMC ratios of the three lot comparisons were close to 1 (Lot A vs. Lot B: 0.82; Lot A vs. Lot C: 0.95; and Lot B vs. Lot C: 1.16). The two-sided 95% CIs for the GMC ratios were within the pre-specified margin of [0.67, 1.5], and therefore lot-to-lot consistency was demonstrated.

Reviewer comment: *Lot-to-lot consistency was demonstrated on the pre-specified analysis population (PPS1). A sensitivity analysis using the PPS2 was similar, but the 95% CI for one pairwise comparison (Lots A and B, 95% CI 0.66, 0.99) was slightly outside of the pre-defined interval. This small difference is unlikely to represent a clinically significant difference in lots. Also of note, the statistical reviewer verified the primary endpoint analyses, but using both the IS and ADIS datasets, calculated slightly different adjusted GMC ratios (95% CIs) for Lots C and A [0.94 (0.77, 1.14)] and Lots C and B [1.14 (0.93, 1.40)]. She verified the sensitivity analyses on different populations and the differences did not change the outcome of the primary analysis.*

6.2.11.2 Analyses of Secondary Endpoints

The analysis of the secondary objective of determining non-inferiority of Sci-B-Vac compared with Engerix-B, as measured by SPR of anti-HBs at Day 196, was based on the PPS2. The table below shows the results of this analysis.

Table 32. Analysis of Seroprotection Rate at Day 196, Four Weeks After the Third Dose, Sci-B-Vac Compared to Engerix-B, Sci-B-Vac, Per Protocol Set 2

Parameter	Pooled Sci-B-Vac N=1778	Engerix-B N=603
Number of subjects evaluated	1753	592
Number of subjects that achieved seroprotection	1740	561
Seroprotection Rate (95% CI[a])	99.3 (98.7, 99.6)	94.8 (92.7, 96.4)
Estimated difference in SPR[b] (95% CI)		4.49 (2.9, 6.6)

Source: 125737/0.0, Sci-B-Vac-002 CSR, Table 22, pp. 75.
Note: Seroprotection was defined as anti-HBs titers ≥10 mIU/mL in serum. Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B and Sci-B-Vac Lot C.
N = total number of subjects in the group; anti-HBs = hepatitis B surface ant body; CI = confidence interval; SPR = seroprotection rate
a Exact (Clopper-Pearson) two-sided confidence interval based on the observed proportion of subjects.
b The estimated difference in proportions [SPR(pooled Sci-B-Vac)-SPR(Engerix-B)] and two-sided 95% CIs were calculated using the Miettinen and Nurminen method.

SPR was 99.3% in the pooled Sci-B-Vac group and 94.8% in the Engerix-B group at Day 196. The difference in SPR (Sci-B-Vac minus Engerix-B) was 4.5%. The lower bound of the 95% CI of the difference in SPR was 2.9%, which was greater than the preset

margin of >−5%. Therefore, non-inferiority of Sci-B-Vac as compared with Engerix-B at Day 196 was demonstrated and the secondary endpoint was met.

Reviewer comment: *The results are consistent with the results observed in the younger age group in Sci-B-Vac-001. Results were also consistent when the analysis was performed on the FAS with and without individuals seropositive at baseline and the ITT.*

6.2.11.3 Subpopulation Analyses

The table below presents the SPR at Day 196, 4 weeks after the third and final dose, in demographic and clinical subpopulations of interest.

Table 33. Seroprotection Rate, Sci-B-Vac Compared to Engerix-B at Day 196, by Subgroup, Sci-B-Vac-002, Per Protocol Set 2

Subgroup	Pooled Sci-B-Vac N	Pooled Sci-B-Vac n	Pooled Sci-B-Vac SPR	Pooled Sci-B-Vac 95% CI	Engerix-B N	Engerix-B n	Engerix-B SPR	Engerix-B 95% CI
Gender								
Male	737	732	99.3	98.4, 99.8	241	225	93.4	89.4, 96.2
Female	1016	1008	99.2	98.5, 99.7	351	336	95.7	93.0, 97.6
Race								
White	1631	1618	99.2	98.7, 99.6	550	520	94.6	92.3, 96.3
Black/African American	82	82	100.0	95.6, 100.0	27	27	100.0	87.2, 100.0
Other	40	40	100.0	91.2, 100.0	15	14	93.3	68.1, 99.8
Ethnicity								
Hispanic/Latino	139	139	100.0	97.4, 100.0	54	49	90.7	79.7, 96.9
Not Hispanic/Latino	1609	1596	99.2	98.6, 99.6	536	510	95.2	92.9, 96.8
Country/Region								
United States	405	400	98.8	97.1, 99.6	138	125	90.6	84.4, 94.9
Canada	77	76	98.7	93.0, 100.0	22	21	95.5	77.2, 99.9
Europe	1271	1264	99.5	98.9, 99.8	432	415	96.1	93.8, 97.7
BMI (kg/m2)								
>30	315	314	99.7	98.2, 100.0	91	80	87.9	79.4, 93.8
≤30	1438	1426	99.2	98.6, 99.6	501	481	96.0	93.9, 97.5
Daily Alcohol Consumption								
≥4 drinks	8	8	100.0	63.1, 100.0	4	4	100.0	39.8 100.0
2-3 drinks	103	103	100.0	96.5, 100.0	42	38	90.5	77.4, 97.3
0-1 drink	1642	1629	99.2	98.7, 99.6	546	519	95.1	92.9, 96.7
Smoking Status								
Current smoker	316	312	98.7	96.8, 99.7	100	88	88.0	80.0, 93.6
Past smoker	346	342	98.8	97.1, 99.7	119	113	95.0	89.4, 98.1
Non-smoker	1090	1085	99.5	98.9, 99.8	373	360	96.5	94.1, 98.1

Source: Adapted from 125737/0.0, Sci-B-Vac-002 CSR, Table 23, pp. 76-77.
Note: Seroprotection was defined as anti-HBs levels ≥10 mIU/mL in serum. Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B and Sci-B-Vac Lot C.
N = total number of subjects evaluated in each group; n = number of subjects who achieved seroprotection;
SPR = seroprotection rate; CI = confidence interval; anti-HBs = hepatitis B surface ant body; BMI = body mass index

SPR point estimates following a three-dose series of Sci-B-Vac were >98% for all subgroups. At CBER's request, the Applicant provided the SPR in 36 Asian subjects in the PPS2, 28 of whom received Sci-B-Vac and 8 of whom received Engerix-B; the SPRs were 100% in both groups.

Reviewer comment: *No multiplicity adjustments were made for subgroup analyses and some subgroups were too small to yield precise estimates or adequate power for hypothesis testing, which was not pre-specified. Therefore, results should be interpreted with caution. All subgroups of young healthy individuals demonstrated high SPRs following Sci-B-Vac. Overall, the subgroup analyses are consistent with trends in vaccine efficacy for the total study population.*

6.2.11.4 Dropouts and/or Discontinuations

With regard to the primary endpoint of lot-to-lot consistency, the PPS1 included 87.9% of the Sci-B-Vac ITT population with a range between Lots A, B, and C of 87.2%-88.8%.

With regard to the secondary endpoint of the SPR following Sci-B-Vac compared to Engerix-B, the PPS2 included 83.6% and 84.7% of the Sci-B-Vac and Engerix-B ITT populations.

Reviewer comment: *A majority of subjects were included in the efficacy analyses populations at 28 days following the third dose, with similar percentages between comparison groups. Thus, dropouts did not significantly affect the efficacy analysis.*

6.2.11.5 Exploratory and Post Hoc Analyses

The table below shows the SPR at specified time points during the study.

Table 34. Seroprotection Rate at Day 168, Day 196, and Day 336 by Vaccine Group, Sci-B-Vac-002, Per Protocol Set 2

Study Day	Pooled Sci-B-Vac N	Pooled Sci-B-Vac n	Pooled Sci-B-Vac SPR (95% CI)	Engerix-B N	Engerix-B n	Engerix-B SPR (95% CI)
168	1775	1605	90.4 (89.0, 91.8)	603	311	51.6 (47.5, 55.6)
196	1753	1740	99.2 (98.7, 99.6)	592	561	94.8 (92.7, 96.4)
336	1718	1695	98.7 (98.0, 99.2)	580	536	92.4 (90.0, 94.4)

Source: 125737/0.0, Sci-B-Vac-002 CSR, Table 25, p. 80.
Note: Seroprotection was defined as anti-HBs titers ≥10 mIU/mL in serum. Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = total number of subjects evaluated in each group; n = number of subjects who achieved seroprotection;
SPR = seroprotection rate; CI = confidence interval; anti-HBs = hepatitis B surface ant body
a The estimated difference in proportions [SPR(pooled Sci-B-Vac)-SPR(Engerix-B)] and two-sided 95% CIs are calculated using the Miettinen and Nurminen method.

Reviewer comment: *A high proportion of young healthy individuals have achieved a seroprotective level of anti-HBs at the time of the third dose of Sci-B-Vac. The SPRs at the various time points did not differ significantly between Sci-B-Vac lots.*

The table below shows the GMCs at specified time points during the study.

Table 35. Analysis of anti-HBs GMC (mIU/mL) at Days 168, 196 and 336, Sci-B-Vac-002, Per Protocol Set 2

Study Day	Pooled Sci-B-Vac N=1778 n	Pooled Sci-B-Vac N=1778 GMC	Engerix-B N=603 n	Engerix-B N=603 GMC
168	1775	118.95	603	14.99
196	1753	5443.07	592	1526.26
336	1718	2093.80	580	473.02

Source: Adapted from 125737/0.0, Sci-B-Vac-001 CSR, Table 26, p. 87.
N = total number of subjects in each group; n = number of subjects evaluated; GMC = geometric mean concentration

Note: Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.

In the pooled Sci-B-Vac group, mean GMCs peaked at 5,443.07 mIU/mL at Day 196 and remained high at Day 336. In the Engerix-B group, mean GMCs peaked at 1,567.22 mIU/mL and remained above the seroprotective level at Day 336.

Reviewer comment: *Sci-B-Vac generated a robust immune response in young healthy individuals that was still apparent approximately 6 months following vaccination. The clinical benefit of higher anti-HBs titers (beyond the seroprotective level) or persistence of anti-HBs above the seroprotective level are not established in the general population.*

6.2.12 Safety Analyses

6.2.12.1 Methods

Descriptive safety analyses were conducted on the Safety Set of all subjects who received at least one dose. Please see sections 6.1.7 and 6.2.7 for a description of active and passive safety monitoring.

6.2.12.2 Overview of Adverse Events

The Safety Set, the primary population for the assessment of safety, included 2,836 subjects total (2,124 in the pooled Sci-B-Vac groups and 712 in the Engerix-B group).

Solicited adverse events

Compliance with individual local, systemic, and other (vital signs, including fever) solicited AE assessment in the 30-minute post-vaccination period was ≥99.4% of subjects vaccinated in each treatment group for each vaccine dose. Compliance with diary card assessments of individual local, systemic, and other (fever) solicited AEs on Day 1 (after the 30-minute post-vaccination assessment) and Days 2 through 7 was ≥90.7% of subjects vaccinated in each treatment group for each vaccine dose.

Reviewer comment: *Because the protocol specified collection of solicited local, systemic and other AEs in the 30-minute post-vaccination period, all subjects in the Safety Set had some post-vaccination solicited AE data collected. The Applicant pre-specified presentation of solicited AEs based on the total number of subjects vaccinated (Safety Set). As diary card completion rates were high, differences in the percentage reporting solicited AEs calculated based on the number of events and subjects who returned diary cards were calculated by the reviewer to be low. As this would not affect the overall risk-benefit profile of the vaccine, the pre-specified analyses are presented here.*

Solicited Local AEs: Overall by subject, all doses considered, at least one solicited local AE was reported by 85.0% and 65.9% of subjects in the Sci-B-Vac (range by lots 82.8%-87.1%) and Engerix-B groups, respectively, and at least one ≥ Grade 3 solicited local AE was reported by 3.4% and 1.4% of subjects in the Sci-B-Vac (range by lots 3.1%-3.6%) and Engerix-B groups, respectively. The numbers and proportions of subjects in the Safety Set reporting any grade and ≥ Grade 3 solicited local AEs are shown below.

Table 36. Incidence of Solicited Local Adverse Events and Maximum Severity Grade 3 and 4 Solicited Local Adverse Events Reported, Day 1 Through Day 7 Following Any Dose, Overall by Subject, Sci-B-Vac-002, Safety Set

Solicited Local Adverse Event Severity (Grade)	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Sci-B-Vac Pooled N=2124 n (%)	Engerix-B N=712 n (%)
Any Solicited Local Adverse Event					
Any Grade	589 (82.8)	602 (85.0)	614 (87.1)	1805 (85.0)	469 (65.9)
Severe (3)	21 (3.0)	20 (2.8)	20 (2.8)	61 (2.9)	8 (1.1)
Potentially life-threatening (4)	4 (0.6)	2 (0.3)	5 (0.7)	11 (0.5)	2 (0.3)
Pain					
Any Grade	527 (74.1)	536 (75.7)	542 (76.9)	1605 (75.6)	384 (53.9)
Severe (3)	8 (1.1)	8 (1.1)	4 (0.6)	20 (0.9)	3 (0.4)
Potentially life-threatening (4)	0	0	0	0	0
Tenderness					
Any Grade	519 (73.0)	535 (75.6)	541 (76.7)	1595 (75.1)	391 (54.9)
Severe (3)	14 (2.0)	15 (2.1)	16 (2.3)	45 (2.1)	5 (0.7)
Potentially life-threatening (4)	0	0	0	0	0
Pruritus/itching					
Any Grade	84 (11.8)	105 (14.8)	92 (13.0)	281 (13.2)	88 (12.4)
Severe (3)	0	2 (0.3)	2 (0.3)	4 (0.2)	2 (0.3)
Potentially life-threatening (4)	0	0	0	0	0
Redness/erythema					
Any Grade	27 (3.8)	20 (2.8)	14 (2.0)	61 (2.9)	12 (1.7)
Severe (3)	1 (0.1)	0	0	1 (0.0)	1 (0.1)
Potentially life-threatening (4)*	4 (0.6)	1 (0.1)	4 (0.6)	9 (0.4)	2 (0.3)
Swelling/edema					
Any Grade	18 (2.5)	15 (2.1)	22 (3.1)	55 (2.6)	6 (0.8)
Severe (3)	1 (0.1)	0	1 (0.1)	2 (0.1)	0
Potentially life-threatening (4)*	0	1 (0.1)	1 (0.1)	2 (0.1)	0

Source: Adapted from 125737/0.0, Sci-B-Vac-002 CSR, Table 36, p. 98 and Table 38, pp. 99-100.
Note: Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects with at least one documented dose; n (%) = number and percent of subjects reporting the adverse event at least once

* Reports of Grade 4/potentially life-threatening erythema and swelling were based on the subject-reported presence of skin necrosis "death of skin cells" or exfoliative dermatitis "peeling over large areas of the skin" at the injection site, while the actual measurement of erythema and edema would be classified as Grade 0 to Grade 1.

Overall by subject, all doses considered, pain and tenderness were the most frequently reported local solicited AEs. IS pain was reported by 75.6% and 53.9% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. IS tenderness was reported by 75.1% and 54.9% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. Grade 3 IS pain and tenderness were uncommon in both study groups. Grade 3 IS pain was reported by ≤1% of study subjects in the pooled Sci-B-Vac and Engerix-B groups. Grade 3 IS tenderness was reported by 2.1% of subjects in the pooled Sci-B-Vac group and 0.7% of subjects in the Engerix-B group.

Reviewer comment: *Clinically significant differences in local reactogenicity were not observed by Sci-B-Vac lots. Local solicited reactogenicity was more common in the Sci-B-Vac group compared to the Engerix-B group, with IS pain and tenderness being notably higher in the Sci-B-Vac group. Severe local reactogenicity was reported in proportionally more subjects in the Sci-B-Vac group compared to the Engerix-B group but was uncommon in both groups. Local reactogenicity in both vaccine groups was higher than that reported in Sci-B-Vac-001, but similar to the rates of local reactogenicity reported in the youngest age group in Sci-B-Vac-001 (18-44 YOA). Any grade pain and*

tenderness were reported at the highest rate following dose 1 of Sci-B-Vac and were reported at slightly lower and similar rates following dose 2 and 3 (not shown).

A total of 13 subjects reported 13 Grade 4 solicited local AEs, 11 subjects who received Sci-B-Vac and 2 subjects who received Engerix-B. All these events were single occurrences of redness/erythema, which accounted for 11 Grade 4 solicited AEs (9 subjects Sci-B-Vac; 2 subjects Engerix-B), or swelling/edema, which accounted for 2 Grade 4 solicited AEs (2 subjects Sci-B-Vac; 0 subjects Engerix-B). Grade 4 local reactogenicity was reported following the first (6 subjects Sci-B-Vac; 1 subject Engerix-B), second (1 subject Sci-B-Vac; 0 subjects Engerix-B) and third dose (4 subjects Sci-B-Vac; 1 subject Engerix-B). Grade 4 local reactogenicity was reported in all Sci-B-Vac lots (4 subjects Lot A; 2 subjects Lot B; 5 subjects Lot C). As per the Applicant, these events were assigned a severity of Grade 4 based on the diary card completed by the subject, indicating (via a check box) the presence of exfoliative dermatitis and/or skin necrosis at the injection site. For one subject, the Grade 4 assignment was based on the study site indicating the presence of exfoliative dermatitis or skin necrosis when assessing redness on the 30-minute post-vaccination assessment without noting the occurrence of redness, measured redness, skin necrosis for swelling, medical attention to the AE, or extension of the visit; the Applicant assessed this to be an error. The recorded measurements of the maximum diameter of redness or swelling during the post-vaccination period in which exfoliative dermatitis and/or skin necrosis were noted were 0 to 50 mm); by measurement, the highest severity of these solicited AEs would be Grade 1. None of the Grade 4 solicited local AEs were medically attended, and no medical treatment was reported. All these AEs resolved with no sequelae. Subjects who reported a Grade 4 solicited local AE following dose 1 or 2, completed the three-dose series with no recurrence of Grade 4 AEs.

Reviewer comment: *Please see the reviewer comment discussing the same safety monitoring issue in Sci-B-Vac-001. Although Grade 4 local solicited AEs were reported more frequently in Sci-B-Vac subjects (0.5%) compared to Engerix-B subjects (0.3%) in Sci-B-Vac-002, they were reported more frequently in Engerix-B subjects (1.0%) compared to Sci-B-Vac subjects (0.4%) in Sci-B-Vac-001. Based on the information provided, it is not anticipated that these reports of Grade 4 local reactogenicity present a safety concern.*

The maximum redness and swelling noted were reported by a 39-year-old man who received dose 1 of Sc-B-Vac Lot A and reported 25.0 cm of redness and swelling Day 3 and 25.0 cm of swelling Day 4. Both were reported as resolved Day 5 and did not recur with subsequent doses. One 29-year-old woman who received dose 2 of Engerix-B reported 15.0 cm of redness Day 2. Other reports of redness or swelling were measured ≤10.0 cm.

Three subjects who received Sci-B-Vac reported local solicited AEs that were medically attended: 1) A 37-year-old man with mild IS pain, moderate myalgia, and an unsolicited AE of severe “neuralgic pain upper arm and chest” for 14 days starting on the day of dose 3, which resolved without treatment; 2) A 45-year-old woman with mild IS pain the day after dose 3, which resolved the same day; and 3) a 39-year-old woman with mild IS pain (also with mild tenderness and pruritus) on the day of and 18 days after dose 1, which resolved and did not recur with the same long duration following additional doses.

Overall, considering all doses, the median durations of pain, tenderness, pruritus, redness, and swelling reported after Sci-B-Vac administration were 2.0, 2.0, 1.0, 1.0, and 2.0 days, respectively. Forty-two subjects in the Sci-B-Vac group (2.0%) reported IS pain continuing beyond the 7-day assessment period (median duration 14.0 days), and nine subjects (0.4%) reported IS pruritus continuing beyond the 7-day assessment period (median duration 8.0 days).

Solicited systemic AEs: Overall by subject, considering all doses, at least one solicited systemic AE was reported by 68.2% and 60.3% of subjects in the Sci-B-Vac and Engerix-B groups, respectively, and at least one ≥ Grade 3 solicited systemic AE was reported by 3.4% and 3.1% of subjects in the Sci-B-Vac and Engerix-B groups, respectively. The number and proportion of subjects in the Safety Set reporting any grade and ≥ Grade 3 individual solicited systemic AEs are shown below.

Table 37. Incidence of Solicited Systemic Adverse Events and Maximum Severity Grade 3 and 4 Solicited Systemic Adverse Events Reported, Day 1 Through Day 7 Following Any Dose, Overall by Subject, Sci-B-Vac-002, Safety Set

Solicited Systemic Adverse Event Severity (Grade)	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Sci-B-Vac Pooled N=2124 n (%)	Engerix-B N=712 n (%)
Any Systemic					
Any	452 (63.6)	500 (70.6)	496 (70.4)	1448 (68.2)	429 (60.3)
Severe (3)	26 (3.7)	27 (3.8)	16 (2.3)	69 (3.2)	22 (3.1)
Potentially life-threatening (4)	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)	0
Nausea/vomiting					
Any	85 (12.0)	87 (12.3)	79 (11.2)	251 (11.8)	86 (12.1)
Severe (3)	1 (0.1)	1 (0.1)	0	2 (0.1)	1 (0.1)
Potentially life-threatening (4)	0	1 (0.1)	0	1 (0.0)	0
Diarrhea					
Any	94 (13.2)	87 (12.3)	96 (13.6)	277 (13.0)	105 (14.7)
Severe (3)	1 (0.1)	4 (0.6)	3 (0.4)	8 (0.4)	0
Potentially life-threatening (4)	0	0	0	0	0
Headache					
Any	255 (35.9)	275 (38.8)	281 (39.9)	811 (38.2)	268 (37.6)
Severe (3)	9 (1.3)	4 (0.6)	3 (0.4)	16 (0.8)	8 (1.1)
Potentially life-threatening (4)	1 (0.1)	0	0	1 (0.0)	0
Fatigue					
Any	266 (37.4)	296 (41.8)	290 (41.1)	852 (40.1)	284 (39.9)
Severe (3)	16 (2.3)	14 (2.0)	5 (0.7)	35 (1.6)	11 (1.5)
Potentially life-threatening (4)	0	0	0	0	0
Myalgia					
Any	289 (40.6)	316 (44.6)	337 (47.8)	942 (44.4)	231 (32.4)
Severe (3)	7 (1.0)	12 (1.7)	7 (1.0)	26 (1.2)	7 (1.0)
Potentially life-threatening (4)	0	0	0	0	0
Fever					
Any	8 (1.1)	9 (1.3)	6 (0.9)	23 (1.1)	8 (1.1)
Severe (3)	0	2 (0.3)	0	2 (0.1)	1 (0.1)
Potentially life-threatening (4)	0	0	1 (0.1)	1 (0.0)	0

Source: Adapted from 125737/0.0, Sci-B-Vac-002 CSR, Table 40, p. 103, Table 42, pp. 104, and 125737/0.27, Table AE_SS_F_ANY.
Note: Implaus ble measurements, body temperature: <=33°C or >=42°C, are removed from the analysis. Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.

N = number of subjects with at least one documented dose; n (%) = number/percentage of subjects reporting the adverse event at least once

Overall by subject, myalgia, fatigue and headache were the most frequently reported local solicited AEs. Myalgia was reported by 44.4% and 32.4% of subjects in the pooled Sci-B-Vac and Engerix-B groups, respectively. Fatigue was reported by 40.1% and 39.9% of subjects in the pooled Sci-B-Vac and Engerix-B groups, respectively. Headache was reported by 38.2% and 37.6% of subjects in the pooled Sci-B-Vac and Engerix-B groups, respectively. Grade 3 or greater systemic reactogenicity was reported in 3.3% and 2.9% of study subjects in the pooled Sci-B-Vac and Engerix-B groups, respectively.

Reviewer comment: *Systemic reactogenicity was reported more commonly in the pooled Sci-B-Vac group compared to the Engerix-B group, attributable to a difference in the frequency of myalgia reported between groups. Severe systemic reactogenicity was uncommon in both groups. By lots, the most commonly reported systemic solicited AEs tended to be reported less frequently in Lot A compared to Lots B and C, most notably myalgia, which was reported in 40.6% of subjects in Lot A compared to 47.8% of subjects in Lot C. The clinical significance of this is not clear as Lot A generated the highest mean GMCs of the three lots. Fever was also reported infrequently and at similar rates between groups (0.9%-1.3%). In general, systemic solicited AEs, were reported at the highest rate following dose 1 of Sci-B-Vac (data not shown). Fever of any grade was reported at a slightly higher rate following dose 3 compared to the first two doses of both Sci-B-Vac and Engerix-B but was reported in <1.0% of subjects after any dose in both groups.*

Systemic reactogenicity in both vaccine groups was higher than that reported in Sci-B-Vac-001, but similar to the rates of systemic reactogenicity reported in the youngest age group in Sci-B-Vac-001 (18-44 YOA). One exception was headache, which was reported less frequently and at similar rates between vaccine groups compared to frequencies of headache observed in subjects 18-44 YOA in Sci-B-Vac-001 (51% Sci-B-Vac, 40.9% Engerix-B).

Three Grade 4 events and one implausible temperature recording were reported, all in subjects who received Sci-B-Vac.

- An 18-year-old woman with no reported medical history reported Grade 4 nausea and vomiting in the setting of an SAE of Vertigo beginning 4 days post-dose 3 of Sci-B-Vac (Lot B), which required hospitalization. The investigator assessed the SAE as unrelated.
- A 45-year-old man with no reported medical history reported a headache which started 3 days post-dose 3 of Sci-B-Vac (Lot A) that increased to Grade 4 headache 6 days post-vaccination and resolved 2 days later. He reported moderate fatigue concurrent with this event. As the solicited AE of headache extended beyond the 7-day assessment, it was recorded as an unsolicited AE of severe intensity and assessed as possibly related. The subject also reported a mild headache of 1 day duration 2 days after the initial headache resolved, which was assessed by the investigator as unrelated. There is no record of a medical encounter with this Grade 4 event, and it appears to be assessed as such by the subject despite not meeting the definition of a Grade 4 event.
- A 31-year-old woman with no pertinent medical history reported a fever, beginning on the day of dose 3 of Sci-B-Vac (Lot C) that increased to a maximum

of 41.2°C (Grade 4) the day after vaccination; the following day temperature was reported at 40.0°C. The fever was 3 days duration in total. She did not report fever following the first two doses. The Grade 4 fever was queried by the clinical site personnel and was confirmed by the subject to be correct. The subject completed the study and did not report unsolicited AEs. The event was not medically attended, but the subject self-medicated with Tylenol 500 mg twice daily.

- A 37-year-old man with asthma reported a fever of 42°C on the day of dose 2 of Sci-B-Vac (Lot B), which was considered implausible as per pre-specified criteria. The subject was afebrile in clinic pre- and post-vaccination and as reported on the diary card the remainder of the post-vaccination period. No unsolicited AEs were reported, and the event was not medically attended. The Applicant reports the AE of fever was assessed by the investigator as mild and very likely associated with vaccine, but the location of this information in the datasets is not apparent to the reviewer. The subject was lost to follow-up after 28 days following dose 2.

Solicited systemic AEs that were medically attended were reported in 12 subjects (0.6%) in the pooled Sci-B-Vac group and 4 subjects (0.6%) in the Engerix-B group. The most common reported medically attended solicited systemic AE was nausea, which was reported by four subjects (0.2%) in the pooled Sci-B-Vac group and one subject (0.1%) in the Engerix-B group. Other medically attended solicited AEs in the Sci-B-Vac group included fatigue (3 subjects), headache (2 subjects), myalgia (1 subject), diarrhea (1 subject), and fever (1 subject).

Overall, considering all doses, the median durations of myalgia, headache, fatigue, diarrhea, nausea/vomiting, and fever reported after Sci-B-Vac administration were 2.0, 1.0, 2.0, 1.0, 1.0, and 1.0 days, respectively. The most common solicited AEs continuing beyond the 7-day assessment period were fatigue (3.5%, 8.0 days median duration), headache (1.9%, 5.0 days median duration), and myalgia (1.8%, 9.0 days median duration).

Reviewer comment: *Fatigue extending beyond the 7-day assessment period was reported slightly more frequently in the pooled Sci-B-Vac group compared to the Engerix-B group (2.1%). Otherwise, the proportion of subjects reporting each solicited systemic AE extending beyond the 7-day assessment period was similar in the two groups.*

Unsolicited adverse events

An overview of unsolicited AEs is presented in the table below and detailed analysis of all unsolicited AEs follows. See sections 6.2.12.3 and 6.2.12.4 for the analyses of deaths and SAEs. Unless otherwise noted, the Sci-B-Vac group refers to the pooled Sci-B-Vac group.

Table 38. Overview of Unsolicited Adverse Events Day 1 to End of Study (Day 336) Unless Otherwise Specified, Sci-B-Vac-002, Safety Set

Adverse Event	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Sci-B-Vac Pooled N=2124 n (%)	Engerix-B N=712 n (%)
Unsolicited AEs within 28 days of any dose	329 (46.3)	358 (50.6)	355 (50.4)	1042 (49.1)	348 (48.9)
Unsolicited vaccine-related AEs within 28 days of any dose*	97 (13.6)	113 (16.0)	112 (15.9)	322 (15.2)	98 (13.8)
MAAE through Day 336	147 (20.7)	151 (21.3)	163 (23.1)	461 (21.7)	125 (17.6)
NOCI (investigator-determined) through Day 336	10 (1.4)	10 (1.4)	13 (1.8)	33 (1.6)	8 (1.1)
AE leading to treatment discontinuation	5 (0.7)	4 (0.6)	2 (0.3)	11 (0.5)	2 (0.3)
Vaccine-related AE leading to treatment withdrawal*	1 (0.1)	2 (0.3)	2 (0.3)	5 (0.2)	1 (0.1)
SAEs within 28 days of dose	2 (0.3)	6 (0.8)	4 (0.6)	12 (0.6)	0
SAEs through Day 336	12 (1.7)	18 (2.5)	12 (1.7)	42 (2.0)	3 (0.4)
Fatal SAE through Day 336	1 (0.1)	0	0	1 (0.0)	0

Source: Adapted from: 125737.0, Sci-B-Vac-002 CSR, Table 35, p. 95
Note: Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects with at least one documented dose; n (%) = number and percent of subjects reporting the adverse event at least once; AE = adverse event; MAAE: medically attended adverse event; NOCI = new-onset chronic illness (investigator-identified); SAE = serious adverse event
* Related was defined as very likely/certain, probably or possibly vaccine-related by the Investigator.

Unsolicited AEs were recorded by all subjects on a diary card, as well as during study visits and the safety phone calls, for 28 days (Days 1-28) following each dose of study vaccine. The Applicant presented serious and non-serious unsolicited AEs together. Solicited AEs that extended beyond the assessment period were also included as unsolicited AEs.

Overall by subject, within 28 days of any study vaccine dose, 49.1% and 48.9% of subjects in the Sci-B-Vac and Engerix-B groups, respectively, reported unsolicited AEs (serious and non-serious). The most frequently reported unsolicited AEs by PT in both the pooled Sci-B-Vac and Engerix-B groups were *Headache* (11.9% and 12.2%, respectively), *Upper respiratory tract infection* (9.2% and 8.8%, respectively), *Nasopharyngitis* (4.9% and 6.3%, respectively), and *Dysmenorrhea* (4.3% and 4.4%, respectively). PTs reported at slightly higher rates in the Sci-B-Vac group compared to the Engerix-B group included *Fatigue* (Sci-B-Vac n=80, 3.8%; Engerix-B n=17, 2.4%) and *Dizziness* (Sci-B-Vac n=31, 1.5%; Engerix-B n=6, 0.8%).

The SOCs with the greatest proportions of subjects reporting unsolicited AEs in the Sci-B-Vac and Engerix-B groups were *Infections and infestations* (21.9% and 23.6%, respectively), *Nervous system disorders* (14.5% in both groups), and *Musculoskeletal and connective tissue disorders* (10.2% and 11.8%, respectively). More unsolicited AEs were reported in the SOC of *General disorders and administration site conditions* in the Sci-B-Vac group compared to the Engerix-B group (9.7% and 6.5%, respectively), due primarily to between-group differences in the HLT of *Injection site reactions* (4.4% and 3.1%, respectively) and the HLT of *Asthenic conditions* (4.0% and 2.5%, respectively), including *Fatigue*.

Reviewer comment: *The overall incidence of unsolicited AEs in the 28 days following vaccination was similar in the two vaccine groups. Fatigue and dizziness occurred more frequently in the Sci-B-Vac group.*

Fatigue is captured as a solicited AE. A majority of unsolicited AEs of fatigue were reactogenicity with duration beyond the assessment period. In Sci-B-Vac-001, and in subjects 18-44 YOA in Sci-B-Vac-001, a between-group imbalance in unsolicited AEs of fatigue within 28 days of vaccination was not seen. With regard to unsolicited AEs of dizziness, a majority were reported within Days 1-4 post-vaccination, and most of those events were assessed as related (23 subjects, 1.1% pooled Sci-B-Vac; 3 subjects, 0.4% Engerix-B). In Sci-B-Vac-001, and in subjects 18-44 YOA in Sci-B-Vac-001, a between-group imbalance in unsolicited AEs of dizziness within 28 days of vaccination was not seen. Subjects in Lot C reported unsolicited AEs of fatigue (5.2%) and dizziness (2.0%) more frequently than other lots of Sci-B-Vac. Reports of the solicited systemic AE of myalgia was also slightly higher in Lot C compared to Lot A; the clinical significance of this is unclear.

In a reviewer-generated SMQ analysis, numerical imbalances in unsolicited AEs within 28 days of vaccination were noted in the following SMQs or sub-SMQs: *Tendinopathies and ligament disorders* (Sci-B-Vac n=23, 1.1%; Engerix-B n=3, 0.4%), *Gastrointestinal nonspecific dysfunction* (Sci-B-Vac n=18, 0.8%; Engerix-B n=2, 0.3%), and *Depression (excluding suicide/self-injury)* (Sci-B-Vac n=11, 0.5%; Engerix B n=0). None of the AEs in the SMQs for *Tendinopathies and ligament disorders* or *Depression (excluding suicide/self-injury)* were assessed as related. *Gastrointestinal nonspecific dysfunction* includes dyspepsia and gastroesophageal reflux disease; three of these AEs in the Sci-B-Vac group and one in the Engerix-B were assessed by investigators as related (possibly or probably).

Reviewer comment: *When considering MAAEs within 28 days of vaccination, PTs in the SMQ for* Tendinopathies and ligament disorders *were more balanced (Sci-B-Vac n=12, 0.6%; Engerix B n=2, 0.3%), None of the unsolicited AEs of* Depression *within 28 days of vaccination were serious and six were medically attended. MAAEs in the SMQ for* Depression (excluding suicide/self-injury) *were reported in similar proportions of subjects in both vaccine groups over the course of the entire study. There is no clear biologic plausibility for a relationship between vaccination and tendinopathies and ligament disorders, or depression.* Gastrointestinal nonspecific dysfunction *within the first week of vaccination (the solicited AE assessment period) was reported in 10 subjects who received Sci-B-Vac and 1 subject who received Engerix-B; this could represent a vaccine reaction, although GI solicited symptoms were reported at similar rates between the Sci-B-Vac and Engerix-B groups. A similar magnitude numerical imbalance with proportionally more subjects in the Engerix-B group reporting unsolicited AEs in the SMQ of* Hepatic disorders*, primarily liver enzyme abnormalities, was observed (9 subjects, 0.4% Sci-B-Vac; 5 subjects, 0.8% Engerix-B). The between-group differences for all the unsolicited AEs noted above are small and may have occurred by chance.*

In each Sci-B-Vac Lot, unsolicited AEs within 28 days of any study vaccine dose were reported by 46.3% (Lot A) – 50.6% (Lot B) of subjects.

Reviewer comment: *PTs of unsolicited AEs were reviewed by Sci-B-Vac lots. No clinically significant differences between lots were identified, except for those identified above (fatigue and dizziness).*

Grade 3, non-serious, unsolicited AEs within 28 days of vaccination were reported by 129 subjects (6.1%) and 33 subjects (4.6%) in the Sci-B-Vac and Engerix-B groups, respectively. The most frequently reported non-serious Grade 3 unsolicited AEs in the Sci-B-Vac group by PT were *Headache* (Sci-B-Vac n=11 subjects, 0.5%; Engerix-B n=3, 0.4%), *Fatigue* (Sci-B-Vac n=11, 0.5%; Engerix-B n=2, 0.3%), *Back pain* (Sci-B-Vac n=8, 0.4%; Engerix-B n=2, 0.3%), and *Myalgia* (Sci-B-Vac n=8, 0.4%; Engerix-B n=1, 0.1%). The most frequently reported non-serious Grade 3 unsolicited AEs in the Engerix-B group by PT were *Upper respiratory tract infection* (Sci-B-Vac n=5, 0.2%; Engerix-B n=7, 1.0%) and *Headache* (see above). The SOCs in both groups with the most frequently reported Grade 3 or greater non-serious unsolicited AEs were *Infections and infestations* (Sci-B-Vac n=33, 1.6%; Engerix-B n=15, 2.1%), *Musculoskeletal and connective tissue disorders* (Sci-B-Vac n=26, 1.2%; Engerix-B n=5, 0.7%), and *Nervous system disorders* (Sci-B-Vac n=21, 1.0%; Engerix-B n=3, 0.4%).

Three subjects reported non-serious unsolicited AEs that were not graded (pyrexia and influenza in the Sci-B-Vac groups and influenza in the Engerix-B group). No non-serious unsolicited AEs were assessed as Grade 4.

Reviewer comment: *Grade 3 non-serious unsolicited AEs consisted mostly of reactogenicity events and were reported slightly more frequently in the pooled Sci-B-Vac group than the Engerix-B group.*

Overall by subject, 322 (15.2%) subjects in the Sci-B-Vac group and 98 (13.8%) subjects in the Engerix-B group reported an unsolicited AE (serious or non-serious) within 28 days following any dose of study vaccine that was assessed as vaccine-related by the investigator. The most frequently reported unsolicited AEs assessed as related by PT were also PTs of solicited AEs; related *Fatigue* was reported more frequently in the Sci-B-Vac group (Sci-B-Vac n=52, 2.4%; Engerix-B n=7, 1.0%), while related *Injection site pain*, *Headache*, and *Myalgia* were reported at similar rates between vaccine groups. Excluding solicited AEs that continued beyond Day 7, the Applicant reported that 10.6% of the Sci-B-Vac group and 10.4% of the Engerix-B group reported vaccine-related unsolicited AEs in the 28-day post-vaccination period. The most common of these vaccine-related unsolicited AEs in the pooled Sci-B-Vac group were *Upper respiratory tract infection* (Sci-B-Vac n=24, 1.1%; Engerix-B n=8 subjects, 1.1%), *Dizziness* (Sci-B-Vac n=23, 1.1%; Engerix-B n=3 subjects, 0.4%), and *Injection site bruising* (Sci-B-Vac n=21, 1.0%; Engerix-B n=7, 1.0%). PTs assessed by investigators as related and reported at lower frequencies than the above events, but in a greater percentage of subjects in the pooled Sci-B-Vac group, included *Back pain* (Sci-B-Vac n=8, 0.4%; Engerix-B n=1, 0.1%) and *Arthralgia* (Sci-B-Vac n=6, 0.3%; Engerix-B n=0). *Arthritis* (both related and overall) was reported at similar rates between groups. A small imbalance in subjects reporting influenza-like illness (ILI) regardless of investigator relationship assessment (Sci-B-Vac n=9, 0.4%; Engerix-B n=0) and related ILI (Sci-B-Vac n=5; Engerix-B n=0) was also noted. In contrast to Sci-B-Vac-001, *Abdominal pain upper* assessed by investigators as related was reported in proportionately more subjects in the Engerix-B group.

Reviewer comment: *In this study,* Dizziness *was reported more frequently within 28 days of vaccination with Sci-B-Vac and was more frequently assessed as related in the Sci-B-Vac group.*

Related, Grade 3, non-serious, unsolicited AEs within 28 days of vaccination were reported in 23 subjects (1.1%) in the pooled Sci-B-Vac group and 7 subjects (1.0%) in the Engerix-B group. In the Sci-B-Vac group these events included reactogenicity events (injection site pain, headache, fatigue, myalgia, diarrhea, and elevated blood pressure) and PTs of *Dizziness* and *Oropharyngeal pain* in one subject (see 6.2.12.7), *Pruritus* generalized and *Swelling face* in one subject (see 8.4.4) and *Influenza-like illness*, *Neuralgia* (in the upper arm and chest for 14 days post-dose 3), *Gastroenteritis*, *Urticaria* (see 8.4.4) and *Pain in jaw* in one subject each.

Medically attended adverse events

MAAEs were collected from the first dose to Day 336. This section discusses medically attended unsolicited AEs. Please see the discussion of solicited AEs that were medically attended above.

MAAEs within 28 days of vaccination were reported in 277 (13.0%) subjects in the Sci-B-Vac group and 76 (10.7%) subjects in the Engerix-B group. The range in the Sci-B-Vac groups was 12.2% (Lot A) to 14.1% (Lot B). In the pooled Sci-B-Vac group, the most frequently reported MAAEs within 28 days of vaccination by PT were *Upper respiratory tract infection* (Sci-B-Vac n=22, 1.0%; Engerix-B n=11, 1.5%), *Sinusitis* (Sci-B-Vac n=16, 0.8%; Engerix-B n=4, 0.6%), *Back pain* (Sci-B-Vac n=13, 0.6%; Engerix-B n=2, 0.3%), and *Urinary tract infection* (Sci-B-Vac n=11, 0.5%; Engerix-B n=7, 1.0%). In the Engerix-B group, the most frequently reported MAAEs within 28 days of vaccination by PT were *Upper respiratory tract infection* (see above), *Urinary tract infection* (see above), *Sinusitis* (see above), and *Nasopharyngitis* (Sci-B-Vac n=5, 0.2%; Engerix-B n=4, 0.6%). Grade 3 or greater, non-serious, MAAEs within 28 days of vaccination were reported in 71 subjects (3.3%) in the pooled Sci-B-Vac groups and 21 subjects (2.9%) in the Engerix-B group. The most frequently reported Grade 3, non-serious, MAAEs by PT in the Sci-B-Vac group were *Back pain* (Sci-B-Vac n=5, 0.2%; Engerix-B n=1, 0.1%), *Sinusitis* (Sci-B-Vac n=5, 0.2%; Engerix-B n=1, 0.1%), and *Anxiety* (Sci-B-Vac n=4, 0.2%; Engerix-B n=0) and in the Engerix-B group were *Upper respiratory tract infection* (Sci-B-Vac n=2, 0.1%; Engerix-B n=7, 1.0%), *Nasopharyngitis* (Sci-B-Vac n=1, 0.0%; Engerix-B n=2, 0.3%), and *Tonsillitis* (Sci-B-Vac n=1, 0.0%; Engerix-B n=2, 0.3%).

From Day 1 to 336, MAAEs were reported in 461 (21.7%) subjects in the pooled Sci-B-Vac group and 125 (17.6%) subjects in the Engerix-B group. The most common unsolicited MAAEs in the Sci-B-Vac group were *Upper respiratory tract infection* (Sci-B-Vac n=33, 1.6%; Engerix-B n=13, 1.8%), *Sinusitis* (Sci-B-Vac n=30, 1.4%; Engerix-B n=4, 0.6%), *Urinary tract infection* (Sci-B-Vac n=19, 0.9%; Engerix-B n=8, 1.1%), and *Back pain* (Sci-B-Vac n=19, 0.9%; Engerix-B n=2, 0.3%). The most common unsolicited MAAEs in the Engerix-B group were *Upper respiratory tract infection* (see above), *Urinary tract infection* (see above), and *Nasopharyngitis* (Sci-B-Vac n=10, 0.5%; Engerix-B n=7, 1.0%). From Day 1 to 336, Grade 3 or greater, non-serious, MAAEs were reported in 109 subjects (5.1%) in the Sci-B-Vac group and 29 subjects (4.1%) in the Engerix-B group. The most commonly reported Grade 3 or greater non-serious MAAEs in the Sci-B-Vac group were *Back pain* (Sci-B-Vac n=7, 0.3% Sci-B-Vac; Engerix-B n=1, 0.1%) and *Sinusitis* (Sci-B-Vac n=5, 0.2%; Engerix-B n=1, 0.1%).

MAAEs assessed by investigators as vaccine-related were reported by 16 subjects (0.8%) in the Sci-B-Vac group and 2 (0.3%) subjects in the Engerix-B group. Related MAAE PTs reported in more than one subject in the Sci-B-Vac group were *Upper respiratory tract infection* (Sci-B-Vac n=3, 0.1%; Engerix-B n=0) and *Dizziness* (Sci-B-Vac n=2, 0.1%; Engerix-B n=0). Additional PTs in the Sci-B-Vac group were *Eyelid edema*, *Nasal congestion*, *Oral pruritus*, *Paresthesia oral*, and "allergic reaction after vaccination" in one subject (see section 8.4.4); *Pruritus generalized* and *Swelling face* in one subject (see section 8.4.4); *Neuralgia* ("neuralgic pain upper arm and chest"), *Myalgia*, and *Injection site pain* in one subject; *Respiratory tract infection* and *Sinusitis* in one subject; and *Gastroenteritis*, *Urinary tract infection*, *Mouth injury*, *Back pain*, *Osteoarthritis*, *Asthma*, *Oropharyngeal pain*, and *Acne* in one subject each. No MAAEs were assessed as related and had a reported onset >28 days following vaccination.

Reviewer comment: *Although there was a trend toward a higher rate of MAAEs in the Sci-B-Vac group during the study, there were no clear patterns that would prompt concern regarding vaccine-related risk.*

<u>New-onset chronic illnesses</u>
NOCIs were collected by the investigator from vaccination to Day 336 and the medical monitor (MM) flagged AEs as NOCIs based on the CDC listing of chronic diseases.

Investigator-determined NOCIs were reported in 33 subjects (1.6%) in the pooled Sci-B-Vac group (range 1.4%-1.8%) and 8 subjects (1.1%) in the Engerix-B group. The MM considered that NOCIs were reported in 14 subjects (0.7%) in the pooled Sci-B-Vac group (range 0.1%-1.0%) and 3 subjects (0.4%) in the Engerix-B group. The assessments of the NOCIs agreed in 11 subjects in the Sci-B-Vac group and 2 subjects in the Engerix-B group. The MM identified 4 events of NOCI not identified by investigators: *Rheumatoid arthritis*, *Blood pressure systolic increased*, and *Hypothyroidism* in one subject each in the Sci-B-Vac group and *Blood pressure diastolic increased* in one subject in the Engerix-B group.

When considering NOCIs that either the investigator or the MM identified, the most frequently reported PTs in the Sci-B-Vac group were *Hypertension* (Sci-B-Vac n=7, 0.3%; Engerix-B n=1, 0.1%) and *Hypothyroidism* (Sci-B-Vac n=4, 0.2%; Engerix-B n=1, 0.1%). No PTs were reported in more than one subject in the Engerix-B group. All NOCIs were assessed as unrelated by investigators.

Reviewer comment: *Percentages of subjects that reported NOCIs were similar in both vaccine groups and low overall.*

Brief narratives of select NOCIs that are potentially immune-mediated are presented here:

- SAE of *Rheumatoid arthritis* (verbatim term "worsening rheumatoid arthritis") and non-serious AE of moderate *Arthralgia* ("hip pain") beginning 93 and 71 days, respectively, post-dose 2 of Sci-B-Vac (Lot A) in a 41-year-old woman with a history of "joint pains" for 3 years prior to enrollment. She reported polyarthralgia at the time of diagnosis, and an ultrasound of the wrists and hands showed synovial proliferation and a small joint effusion without acute inflammation. She had laboratory tests showing a positive antinuclear antibody with positive Anti-Scl70, negative rheumatoid factor, and normal C-reactive protein. She was treated with ibuprofen, meloxicam, and methotrexate. The investigator assessed

the event as serious because it was medically significant and assessed the SAE as not related to study vaccination. She discontinued from treatment and the study on Day 175, prior to dose 3 due to these events.

- Non-serious AE of Sarcoidosis of moderate intensity starting on an unknown date approximately 51 days following dose 3 of Sci-B-Vac (Lot C) in a 39-year-old woman with ongoing facial numbness since approximately 4 months prior to vaccination. Diagnosis included a chest X-ray, chest CT scan, and pulmonary function tests, the results of which were not reported. The investigator assessed the NOCI as unrelated to study vaccination.
- A 36-year-old man (as reported in the datasets) with an ongoing history of hyperlipidemia, asthma, gender reassignment, post-traumatic stress disorder, depression, bipolar disorder, attention deficit/hyperactivity disorder, insomnia, back pain and a herniated disc was being treated with atorvastatin, estradiol, finasteride, Adderall, citalopram, prazosin, tramadol, and meloxicam. The subject was diagnosed with severe postural orthostatic tachycardia syndrome and moderate dysphagia, both of which were considered unlikely unrelated NOCIs by the investigator, 77 days post-dose 3 of Sci-B-Vac (Lot C). He was treated with propranolol and ondansetron. No other unsolicited AEs were reported by the subject.

Reviewer comment: *Sjögren's syndrome can be associated with autonomic instability (Ng, 2012) and dry mouth could lead to dysphagia (Ng, 2012). The Applicant reported that they had no additional information regarding underlying causes of the postural orthostatic tachycardia syndrome and dysphagia and attributed the AEs to concomitant medications taken for several concurrent medical conditions, which could have contributed to these NOCIs.*

Additional potentially immune-mediated NOCIs include hypothyroidism (reported in four subjects, 0.2% in the Sci-B-Vac and one subject, 0.1% in the Engerix-B group). One subject who received Sci-B-Vac reported two unsolicited AEs of iritis, which were not NOCIs, but are mentioned here because of the potential association with systemic inflammatory diseases. In this subject moderate iritis was reported on an unknown date approximately 2 months and 3 months following the third dose. The events were medically attended, but no treatment was reported. Both events resolved and no other unsolicited AEs were reported. The investigator assessed both events as unrelated. Based on the information provided, the etiology of these events is unclear.

6.2.12.3 Deaths

One death was reported from Day 1 to Day 336. A 35-year-old man who reported no medical history and no medications at enrollment, received the first dose of Sci-B-Vac Lot A and died of sudden cardiac death (b) (6 days later. A post-mortem examination revealed evidence of past open-heart surgery and biventricular hypertrophy. Autopsy and toxicological examination determined the cause of death to be sudden cardiac death due to hypertrophic heart disease. The death was assessed as unrelated to study vaccine by the investigator.

Reviewer comment: *Although there is a temporal relationship with vaccination, the history of prior cardiac surgery and hypertrophic heart disease indicates a chronic condition that can result in sudden cardiac death. The reviewer agrees with the investigator's assessment that this death was unlikely related to vaccination. No subjects*

reported SAEs in this study in the Cardiac Disorders *SOC and only one subject reported an MAAE in the* Cardiac Disorders *SOC, severe tachycardia in the setting of decompensated alcoholic liver disease. Within 28 days of vaccination, four subjects (0.2%) in the Sci-B-Vac group and one subject (0.1%) in the Engerix-B group reported non-medically attended unsolicited AEs in the Cardiac SOC, including tachycardia, extrasystoles and palpitations.*

6.2.12.4 Nonfatal Serious Adverse Events

All SAEs were monitored through Day 336, approximately 6 months following the third dose. A summary of SAEs occurring up to 30 days following any dose and throughout the study period is below. The Applicant's summary of SAEs included the fatal SAE described in section 6.2.12.3.

Table 39. Treatment-Emergent SAEs Within 28 Days of Any Dose of Study Vaccine and Day 1 Through Day 336, Sci-B-Vac-002, Safety Set

Adverse Event	Sci-B-Vac Lot A N=711 n (%)	Sci-B-Vac Lot B N=708 n (%)	Sci-B-Vac Lot C N=705 n (%)	Sci-B-Vac Pooled N=2124 n (%)	Engerix-B N=712 n (%)
SAEs within 28 days following any dose	2 (0.3)	6 (0.8)	4 (0.6)	12 (0.6)	0
SAEs Day 1-Day 336	12 (1.7)	18 (2.5)	12 (1.7)	42 (2.0)	3 (0.4)
Fatal SAE Day 1-Day 336	1 (0.1)	0	0	1 (0.05)	0
Related SAE within 28 days following and dose*	0	0	0	0	0
Related SAE Day 1-Day 336*	0	0	0	0	0

Source: Adapted from 125737/0.0, Sci-B-Vac-002 CSR, Table 35, pp. 95 and Sci-B-Vac-002 Tables, Figures, Listings, Table 14.3.1.3.1, pp. 4657-4683.
Note: Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects with at least one documented dose; n (%) = number and percent of subjects reporting the adverse event at least once; SAE = serious adverse event
* Related was defined as very likely/certain, probably or possibly vaccine-related by the Investigator.

Up to 28 days following any dose of study vaccine, 12 subjects (0.6%) in the Sci-B-Vac arm and 0 subjects in the Engerix-B group reported SAEs. One PT was reported as an SAE during this time period by more than one subject: *Appendicitis* (two subjects in the Sci-B-Vac group). One subject was a 42-year-old man who presented with appendicitis 4 days following dose 1. The second subject was a 41-year-old man with no medical history who presented with appendicitis 27 days following dose 1. Both subjects received doses 2 and 3. An additional SAE of appendicitis was reported in a 42-year-old man 58 days post-dose 3. The first event was assessed as unlikely related to vaccine and the other two SAEs of appendicitis were assessed as unrelated by investigators. In addition, two subjects reported SAEs of vertigo, one with a PT of *Vertigo* (reported in an 18-year-old woman with an elevated WBC 4 days after the third dose and treated with steroids) and another subject with a PT of *Vertigo positional* (reported in a 44-year-old woman 1 day after the third dose). The remainder of the SAEs reported within Days 1-28 post-vaccination occurred in the Sci-B-Vac group and had the following PTs: *Sudden cardiac death* (see section 6.2.12.3), *Alcoholic liver disease*, *Chlamydial infection*, *Cholecystitis chronic*, *Gastrointestinal arteriovenous malformation*, *Joint dislocation*, *Pneumonia*, and *Spinal compression fracture*.

Reviewer comment: *Within 28 days of any dose, few subjects reported SAEs following Sci-B-Vac and no subjects reported SAEs following Engerix-B. Although, three subjects reported* Appendicitis *within 2 months of vaccination with Sci-B-Vac, the timing of onset was distributed throughout that time period, suggesting this may have occurred by chance. With regard to the SAEs of vertigo, the underlying pathologies of these two SAEs are distinct. Please also see the discussion of SAEs in section 8.4.2.*

During the study period, 42 subjects (2.0%) in the Sci-B-Vac group and 3 subjects (0.4%) in the Engerix-B group reported SAEs. Three SAE PTs were reported in more than one subject in the Sci-B-Vac group: *Appendicitis* (3 subjects in the Sci-B-Vac group, 0 in the Engerix-B group, see discussion above), *Intervertebral disc protrusion* (3 subjects in the Sci-B-Vac group, 0 in the Engerix-B group), and *Erysipelas* (2 subjects in the Sci-B-Vac group, 0 in the Engerix-B group). No SAE PTs were reported in more than one subject in the Engerix-B group. The SOCs with the greatest proportions of subjects reporting SAEs were *Infections and infestations* (Sci-B-Vac n=13, 0.6%; Engerix-B n=0), *Injury, poisoning, and procedural complications* (Sci-B-Vac n=10, 0.5%; Engerix-B n=1, 0.1%), and *Musculoskeletal and connective tissue disorders* (Sci-B-Vac n=6, 0.3%; Engerix-B n=0). No SAEs were assessed by investigators as related.

Of note, one subject, a 43-year-old woman, reported an SAE of *Stress cardiomyopathy* 152 days post-dose 3. Coronary angiography showed "patent coronary arteries and band-like akinesia of the central ventricle suggestive of Takotsubo cardiomyopathy."

Reviewer comment: *There was a numerical imbalance in overall SAEs reported during the study period. However, the number of SAEs reported in both groups was small. The narratives were reviewed and do not have a pattern of timing or pathology suggesting relationship to vaccination. The timing of onset of the event of cardiomyopathy is also not suggestive of a vaccine-associated myocarditis.*

6.2.12.5 Adverse Events of Special Interest (AESI)

Not applicable.

6.2.12.6 Clinical Test Results

Subjects at select sites in Canada and the US were enrolled in the clinical laboratory sub-study, which assessed hematology and biochemistry parameters pre-vaccination (V1), and 7 days following each dose (Days 7, 35 and 175). In total 393 subjects of 4,452 subjects in the Safety Set (13.9%) were included in the clinical laboratory subset (SSA Set, 297 subjects in the pooled Sci-B-Vac and 96 subjects in the Engerix-B group).

Hematology evaluations included hemoglobin, platelet count, WBC count with differential, mean cell hemoglobin, mean cell hemoglobin concentration, and mean corpuscular volume. No clinically significant changes from pre-vaccination to each post-vaccination time point were observed based on mean values of each of the hematologic parameters.

The following are the number and proportion of subjects in the SSA Set with hematologic changes from pre-vaccination (normal to Grade 2) to ≥Grade 3 or post-vaccination:

- Hemoglobin value: pooled Sci-B-Vac (2 subjects, 0.7%); Engerix-B (2 subjects, 2.1%)

- Hemoglobin decreased from baseline: pooled Sci-B-Vac (5 subjects, 1.7%); Engerix-B (4 subjects, 4.2%)
- Lymphocytes decreased: pooled Sci-B-Vac (0 subjects); Engerix-B (1 subject, 1.0%)

Based on all unsolicited AEs reported within 28 days of vaccination on all subjects, 12 subjects (0.6%) in the Sci-B-Vac group and 5 subjects in the Engerix-B group (0.7%) had treatment-emergent hematologic abnormalities considered to be clinically significant by investigators. Anemia and related PTs were the most commonly reported hematologic abnormality AE (Sci-B-Vac n=9, 0.4%; Engerix-B n=4 subjects, 0.6%). Two events in the Sci-B-Vac group were assessed by investigators as vaccine-related: a mild neutropenia, and a mild elevation in platelets. One subject who received Sci-B-Vac was discontinued one month after dose 1 for "worsening anemia" (moderate at screening progressing to severe) occurring at an unknown time following vaccination; the anemia was assessed as unrelated to vaccination. No hematologic abnormalities were serious.

Biochemistry evaluations included BUN, serum creatinine, AP, ALT, AST, total and conjugated bilirubin and GGT. No clinically significant changes from pre-vaccination to each post-dose time point were observed based on mean values of each of the biochemistry parameters.

The following are the number and proportion of subjects in the SSA Set with hematologic changes from pre-vaccination (normal to Grade 2) to ≥ Grade 3 or post-vaccination:

- AST: One subject, a 35-year-old man in the pooled Sci-B-Vac group, had a shift from normal to Grade 4 on Day 35, which decreased to a Grade 1 nine days later. AEs of Heat exhaustion and Blood creatine phosphokinase increased are also reported 3 and 7 days after the onset of the AST elevation. The investigator assessed the elevated AST as mild.
- Bilirubin: Two subjects (0.7%) in the pooled Sci-B-Vac group had shifts. A 40-year-old woman's bilirubin increased from Grade 1 pre-vaccination to Grade 3 on Day 175. A 21-year-old woman's bilirubin increased from normal pre-vaccination to Grade 4 on Day 175. No unsolicited AEs are reported for either subject.

  Reviewer comment: *Both bilirubin abnormalities appear to the reviewer to be potential errors in the reported normal range in the datasets.*

- BUN: Three subjects (1.0%) in the Sci-B-Vac group (all Lot A) had BUN shifts – two subjects had shifts from normal to Grade 3 on Day 7 and one subject had a shift from Grade 2 to 3 on Day 175. One subject (1.0%) in the Engerix-B group had a shift from Grade 1 to 3 on Day 7. No AEs other than the abnormal laboratory value were reported in these subjects.

Based on all unsolicited AEs reported within 28 days of vaccination on all subjects, 10 subjects (0.5%) in the Sci-B-Vac group and 6 subjects (0.8%) in the Engerix-B group had treatment-emergent biochemistry abnormalities considered to be clinically significant by investigators. Liver enzyme elevations and related PTs were the most commonly reported biochemical abnormality AE (Sci-B-Vac n=7, 0.3%; Engerix-B n=5, 0.7%). One event in the Sci-B-Vac group was assessed by the investigator as possibly related: a moderate decrease in glomerular filtration rate in a 43-year-old man. None of the AEs

associated with abnormal biochemistry values were serious and none led to treatment discontinuation.

Reviewer comment: *There were no trends in clinically significant laboratory abnormalities to suggest toxicity with Sci-B-Vac compared with Engerix-B.*

Vital signs: The Applicant monitored vital signs pre- and 30-minutes post-vaccination ('other" solicited AEs) and graded abnormalities as per the FDA guidance (FDA, 2007). Please see section 6.2.12.2 for an assessment of fever. The number and proportion of subjects with post-vaccination vital signs, other than temperature, out of normal range is shown in the table below.

Table 40. Solicited "Other" Adverse Events Assessed 30 Minutes Following Any Dose, by Treatment Group, Sci-B-Vac-002, Safety Set

Solicited "Other" Adverse Event	Sci-B-Vac Lot A N=711	Sci-B-Vac Lot B N=708	Sci-B-Vac Lot C N=705	Sci-B-Vac Pooled N=2124	Engerix-B N=712
Hypotension (systolic)	3 (0.4)	6 (0.8)	5 (0.7)	14 (0.7)	8 (1.1)
Hypertension (systolic)	82 (11.5)	78 (11.0)	90 (12.8)	250 (11.8)	87 (12.2)
Hypertension (diastolic)	76 (10.7)	50 (7.1)	81 (11.5)	207 (9.7)	78 (11.0)
Tachycardia (beats/min)	5 (0.7)	4 (0.6)	7 (1.0)	16 (0.8)	9 (1.3)
Bradycardia (beats/min)	80 (11.3)	107 (15.1)	87 (12.3)	274 (12.9)	92 (12.9)
Respiratory Rate (Breaths/min)	83 (11.7)	91 (12.9)	93 (13.2)	267 (12.6)	83 (11.7)

Source: 125737/0.0, Sci-B-Vac-002 CSR, Table 44, p. 106.
Note: Pooled Sci-B-Vac includes the Sci-B-Vac Lot A, Sci-B-Vac Lot B, and Sci-B-Vac Lot C.
N = number of subjects receiving the specified dose; n (%) = number and percent of subjects reporting the adverse event at least once; SAE = serious adverse event

Two subjects in the Sci-B-Vac group (Lot C) had a medically attended "other" solicited AE of systolic hypertension – a 45-year-old woman with mild systolic hypertension pre- and post-dose 2, increased from normal prior to dose 1 and a 39-year-old man with mild systolic hypertension since prior to dose 1.

Reviewer comment: *Similar proportions of subjects reported vital sign abnormalities post-vaccination in the pooled Sci-B-Vac and Engerix-B groups. The Applicant presented proportions of subjects with post-vaccination vital sign abnormalities by severity and dose (not shown). No clinically significant between-group differences were identified.*

6.2.12.7 Dropouts and/or Discontinuations

In the pooled Sci-B-Vac and Engerix-B groups, 7.5% and 5.8% of subjects did not receive all three doses. Eleven (0.5%) and two (0.3%) subjects, respectively, discontinued treatment due to an AE. Five subjects (0.2%) in the pooled Sci-B-Vac group and 1 subject (0.1%) in the Engerix-B group were withdrawn for AEs considered at least possibly related:

- Non-serious, severe dizziness and oropharyngeal pain (verbatim term "sore throat") reported on the day of dose 1 of Sci-B-Vac (Lot C), resolving after 2 days in a 19-year-old woman with a past medical history of anorexia and a current history of iron deficiency anemia associated with palpitations, and migraine. Severe headache and myalgia were also reported. She reported nasopharyngitis 15 days prior to study vaccination, resolving the day prior to vaccination. The subject was seen in the emergency room for these symptoms. She received

paracetamol, chlorphenamine, and sumatriptan during the episode. All symptoms resolved 2 days after vaccination. The AEs were assessed by the investigator as probably related, and the subject requested to discontinue.

- Non-serious, moderate, medically attended (doctor visit) "arthritis of the left ankle" (PT Osteoarthritis) reported 5 days after dose 2 of Sci-B-Vac (Lot B), assessed as possibly related, resolved 4 days later, in a 43-year-old woman with no reported medical history. The subject reported influenza-like illness (no fever is reported), assessed as possibly related, in the first week after dose 1 and neck and shoulder pain 1 week post-dose 1, which resolved the day prior to dose 2. The arthritis was treated with etoricoxib and diclofenac.
- Non-serious, severe injection site pain, assessed as possibly related, and non-serious, severe myalgia, assessed as unlikely related, reported 6 days after dose 2 of Sci-B-Vac (Lot C) and resolved 2 days later in a 40-year-old woman. The myalgia was treated with ibuprofen and the events were not medically attended. She was lost to follow-up 6 months later.
- Solicited AE of severe fatigue and unsolicited AEs of mild depressed mood and severe back pain (verbatim term "worsening back pain"), both assessed as unlikely related to vaccination, following dose 2 of Sci-B-Vac (Lot A) in a 45-year-old woman with a several-year history of back, bilateral paraspinal, and shoulder pain. She reported moderate to severe fatigue of 3 days duration post-dose 1 and mild to severe fatigue beginning the day after dose 2. As a solicited AE, the fatigue was considered related. All events resolved within 5 days without treatment.
- Solicited AE of mild to moderate fatigue reported of 7 days duration post-dose 1 and mild to moderate fatigue reported 3 days duration post-dose 2 of Sci-B-Vac (Lot B) in a 41-year-old man.
- Solicited AEs of mild fatigue, headache and IS pruritus, beginning the day of dose 2 of Engerix-B, resolving within 1-3 days without treatment in a 37-year-old woman. This subject also reported "hot flashes" of 2 days duration post-dose 1, assessed as possibly related, but did not discontinue treatment due to this unsolicited AE.

Unrelated or unlikely related AEs (serious and non-serious) that led to treatment discontinuation were reported in six subjects in the pooled Sci-B-Vac group and one subject in the Engerix-B group:

- Sudden cardiac death reported (b) (6) days post-dose 1 of Sci-B-Vac (Lot A) (see section 6.2.12.3).
- SAE of *Rheumatoid arthritis* (verbatim term "worsening rheumatoid arthritis") and Non-serious AE of moderate *Arthralgia* ("hip pain") beginning 93 and 71 days, respectively, post-dose 2 of Sci-B-Vac (Lot A) in a 41-year-old woman with a history of "joint pains" for 3 years prior to enrollment. The investigator assessed the event as serious because it was medically significant and assessed it as not related to study vaccination. Please see section 6.2.12.2 (NOCIs) for additional details.
- Migraine (verbatim term "worsening of migraine") of moderate severity on an unknown start date in the month of and following dose 1 of Sci-B-Vac (Lot B) (imputed to be the day of vaccination) in a 23-year-old woman with a history of migraines.
- Anemia (verbatim term "worsening of anemia"), progressing from moderate to severe by investigator assessment (results not provided) on an unknown date in

a subject who received dose 1 of Sci-B-Vac (Lot B) and was discontinued one month later (see section 6.2.12.6).

- Dizziness of moderate severity and medically attended, starting 10 days post-dose 1 of Sci-B-Vac (Lot A), which was ongoing at study discontinuation 21 days later, in a 44-year-old woman with asthma, hypertension, and depression.
- NOCI of Arnold Chiari malformation, assessed as severe, diagnosed 58 days post-dose 2 of Sci-B-Vac (Lot A) and treated with surgical decompression 2 months later, in a 38-year-old woman with a medical history of seasonal allergy.
- SAE of DVT starting 115 days post-dose 2 of Engerix-B in a 44-year-old man with a family history of pulmonary embolism and who reported prolonged sitting.

In the pooled Sci-B-Vac and Engerix-B groups, 10.7% and 9.7% of subjects, respectively, withdrew before completing the study (before Day 336). AEs (serious and non-serious) leading to study withdrawal were reported in 0.4% Sci-B-Vac (8 subjects) and 0.1% (1 subject) in the Engerix-B group. SAEs and non-serious AEs that led to both treatment discontinuation and study withdraw, and are described above, included the PTs of dizziness, oropharyngeal pain and headache (related) in one subject; osteoarthritis (related); sudden cardiac death; rheumatoid arthritis; migraine; anemia; dizziness; and Arnold Chiari malformation in the pooled Sci-B-Vac group and headache, fatigue, and IS pruritus (related) in one subject in the Engerix-B group.

6.2.13 Study Summary and Conclusions

Sci-B-Vac-002 was a Phase 3, multi-center, multi-national, double-blind, randomized, active-controlled trial to evaluate the manufacturing consistency, immunogenicity and safety of Sci-B-Vac. A total of 2,836 HBV vaccine-naïve adults 18-45 YOA were enrolled and received at least one dose of a three-dose series of one of three independent lots of Sci-B-Vac or Engerix-B administered on Days 1, 28, and 168. The primary objective was evaluation of manufacturing equivalence as determined by the three GMC ratios of anti-HBs at Day 196, 4 weeks after the third dose, between the three Sci-B-Vac lot groups. The secondary objective was demonstration of non-inferiority of Sci-B-Vac to Engerix-B at Day 196. Subjects were followed for safety and immunogenicity from first vaccination through Day 336, approximately 6 months following the third dose of vaccine.

For the primary endpoint of lot-to-lot consistency, mean adjusted GMCs of anti-HBs at Day 196 were 5,882.25 mIU/mL, 4,821.65 mIU/mL, and 5,569.89 mIU/mL across Lots A, B, and C of Sci-B-Vac, respectively. The GMC ratios (95% CIs) among the three lot groups were Lot A vs. Lot B: 0.82 (0.67, 1.00), Lot A vs. Lot C: 0.95 (0.78, 1.15); and Lot B vs. Lot C: 1.16 (0.95, 1.41). Lot-to-Lot consistency was demonstrated because the two-sided 95% CIs for the GMC ratios between lots were within the pre-specified margin of [0.67, 1.5]. For the secondary endpoint of non-inferiority, the SPR was 99.3% (95% CI: 98.7, 99.6) in the pooled Sci-B-Vac group and 94.8% (95% CI: 92.7, 96.4) in the Engerix-B group, resulting in a difference in SPR (pooled Sci-B-Vac−Engerix-B) of 4.5%. The LB of the 95% CI of the difference in SPR was 2.9%, greater than the preset non-inferiority margin of -5%. Therefore, non-inferiority of Sci-B-Vac compared with Engerix-B 4 weeks after the third dose (in subjects 18-45 YOA) was demonstrated.

As in Sci-B-Vac-001, IS pain and tenderness were the most commonly reported solicited local symptoms after Sci-B-Vac administration, reported in a majority of subjects and at greater frequencies than in the Engerix-B group. Myalgia, headache, and fatigue were the most commonly reported solicited systemic symptoms after Sci-B-Vac

administration. Myalgia was the only solicited AE reported more frequently in the Sci-B-Vac group compared to the Engerix-B group. Fever was uncommon. In general, local and systemic solicited symptoms tended to be reported at the highest frequencies in the Sci-B-Vac group following the first dose.

SAEs were reported more frequently during the study in the Sci-B-Vac group compared to the Engerix-B group. One death was reported in a 35-year-old man who died of sudden cardiac death due to hypertrophic heart disease (b) (6) days after dose 1 of Sci-B-Vac, which was assessed by the investigator as unrelated. Otherwise, SAEs were generally typical of the age and health of the study population, with infections and injuries being the most commonly reported class of event. The nature or timing of the SAEs did not suggest a vaccine-related safety concern.

7. Integrated Overview of Efficacy

An integrated analysis of efficacy was not performed as the two pivotal trials, Sci-B-Vac-001 and Sci-B-Vac-002, had different randomization schemes (1:1 and 1:1:1:1, respectively) and included different study populations (adults ≥18 YOA and adults 18-45 YOA, respectively). Please see the efficacy analysis of the individual studies in 6.1.11 and 6.2.11.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

The ISS, submitted by the Applicant, included results from a pooled analysis of the two pivotal clinical trials delineated in section 8.2.1 below. Please see the reviews of the individual trials in sections 6.1 and 6.2.

Despite differences between the two pivotal trials (study populations differed in age and presence of chronic diseases), integration of the safety data from these populations was performed to increase the likelihood of identifying uncommon events related to vaccination that might not be evident from individual studies enrolling smaller numbers of subjects. It also allowed for pooling of safety data in subgroups to increase the power to evaluate safety and is considered supplementary to the safety analyses performed on the individual study populations.

The integrated analysis will focus on SAEs, unsolicited AEs, MAAEs, and NOCIs. Please see the individual studies for analyses of solicited AEs.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Integration of Sci-B-Vac-001 and Sci-B-Vac-002 for safety analyses was possible because of the following similarities in study design:

- Subjects in both studies received a three-dose series of Sci-B-Vac 10 mcg/1.0 mL or Engerix-B 20 mcg/1.0 mL IM on Days 1, 28, and 168.
- Studies were both randomized, active-controlled, and double-blind.
- Safety data was collected similarly in both studies, including AEs recorded by subjects on diary cards in the 28 days following each dose and spontaneously

reported by subjects at clinic visits. The visit schedules were identical except that in Sci-B-Vac-002 one clinic visit was replaced by a safety phone call.
- Total safety follow-up time was until Day 336, approximately 6 months after the third dose. SAEs, MAAEs, and NOCIs were recorded in both studies from Day 1-336.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The pooled safety dataset from the two pivotal clinical trials consisted of 4,443 subjects in the Safety Analysis Set, all subjects who received at least one dose of study vaccine. This included 2,920 subjects who received at least one dose of Sci-B-Vac and 1,523 who received at least one dose of Engerix-B.

Exposure

The table below shows the distribution of subjects that received exactly 1, 2, and 3 doses of Sci-B-Vac or Engerix-B in the pooled dataset.

Table 41. Vaccine Exposure by Vaccine Group, Integrated Summary of Safety, Safety Analysis Set

Total number of doses received	Sci-B-Vac N=2920 n (%)	Engerix-B N=1523 n (%)
1 dose	70 (2.4)	20 (1.3)
2 doses	125 (4.3)	47 (3.1)
3 doses	2725 (93.3)	1456 (95.6)

Source: Adapted from 125737/0.0, ISS, Table 8, p. 28
N = total number of subjects in each group; n (%) = number and percent of subjects receiving the specified total number of doses

In the Safety Analysis Set in the pooled analysis, 93.3% of subjects vaccinated received all three doses of Sci-B-Vac. A slightly higher proportion of subjects vaccinated received all three doses of Engerix-B (95.6%).

Reviewer comment: *More subjects in the Sci-B-Vac group withdrew from treatment due to pregnancy (0.5% Sci-B-Vac; 0.1% Engerix-B) and other reasons (5.7% Sci-B-Vac; 3.7% Engerix-B), which primarily included consent withdrawal and loss to follow-up. Please see the individual studies for details.*

Demographic, Medical, and Behavioral Characteristics

The table below shows the demographic composition of the pooled analysis.

Table 42. Demographic and Other Baseline Characteristics, Safety Analysis Set

Demographic Variable	Sci-B-Vac N=2920 n (%)	Engerix-B N=1523 n (%)
Gender		
Male	1222 (41.8)	594 (39.0)
Female	1698 (58.2)	929 (61.0)

Demographic Variable	Sci-B-Vac N=2920 n (%)	Engerix-B N=1523 n (%)
Race		
White	2656 (91.0)	1384 (90.9)
Black or African American	189 (6.5)	103 (6.8)
Asian	45 (1.5)	13 (0.9)
American Indian or Alaska Native	11 (0.4)	6 (0.4)
Native Hawaiian or other Pacific Islander	1 (0.0)	0
Other	18 (0.6)	17 (1.1)
Race Group		
White	2656 (91.0)	1384 (90.9)
Black or African American	189 (6.5)	103 (6.8)
Asian	45 (1.5)	13 (0.9)
Other	30 (1.0)	23 (1.5)
Ethnicity		
Hispanic or Latino	274 (9.4)	149 (9.8)
Non-Hispanic or Latino	2638 (90.3)	1368 (89.8)
Not collected per local guidelines	8 (0.3)	6 (0.4)
Age at informed consent (years)		
Mean	39.8	45.8
SD	14.10	16.15
Median	38.0	43.0
Minimum	18	18
Maximum	86	90
Age Group		
18-44 years	2192 (75.1)	844 (55.4)
45-64 years	432 (14.8)	383 (25.1)
≥65 years	296 (10.1)	296 (19.4)
65-74 years	243 (8.3)	250 (16.4)
75-84 years	51 (1.7)	45 (3.0)
≥85 years	2 (0.1)	1 (0.1)
BMI Category		
≤30 kg/m2	2236 (76.6)	1114 (73.1)
>30 kg/m2	684 (23.4)	409 (26.9)
Diabetes status		
Diabetes	61 (2.1)	65 (4.3)
Non-Diabetes	2859 (97.9)	1458 (95.7)
Smoking status/Tobacco use		
Current smoker/tobacco user	510 (17.5)	249 (16.3)
Former smoker/tobacco user	607 (20.8)	365 (24.0)
Non-smoker/non-tobacco user	1802 (61.7)	909 (59.7)
Average Daily Alcohol Consumption		
0-1 drink/day	2725 (93.3)	1397 (91.7)
2-3 drinks/day	179 (6.1)	117 (7.7)
≥4 drinks/day	16 (0.5)	9 (0.6)

Source: Adapted from 125737/0.0, Integrated Summary of Safety, Table 10, pp. 35-37.
N = total number of subjects in each group; n (%) = number and percent of subjects with the demographic, clinical, or behavioral characteristic; BMI = body mass index

Across both vaccine groups, vaccinated subjects were majority female (58.2-61.0%), White (90.9-91.0%), and non-Hispanic or Latino (89.8-90.3%). Subjects in the Sci-B-Vac

group were younger, with a mean (SD) and median age of 39.8 years (14.10) and 38.0 years compared to 45.8 years (16.15) and 43.0 years in the Engerix-B group.

Because the proportions of subjects in some racial groups were small, for the pooled safety analysis by race, the Applicant grouped subjects into the following groups: Black or African American, Asian, White, and Other (1.2% of the total pooled population, including American Indian or Alaska Native, Native Hawaiians or Pacific Islander, or Other).

Reviewer comment: *Sci-B-Vac-002, the lot-to-lot consistency trial, was the largest of the two pivotal trials. As only subjects 18-45 YOA were enrolled in this study and the randomization ratio was 3:1 (Sci-B-Vac:Engerix-B), the Sci-B-Vac group in the pooled analysis is notably younger than the Engerix-B group. Only healthy subjects were included in Sci-B-Vac-002; therefore, the Sci-B-Vac group in the pooled analysis also has smaller proportions of subjects with obesity and diabetes than the Engerix-B group, although the differences between groups is relatively small.*

8.2.3 Categorization of Adverse Events

For this pooled safety analyses, as in the individual studies, MedDRA version 20.1 was used. For the reviewer's analysis of potentially immune-mediated events, the MedDRA version 23.1 was used as it contained the SMQ for potentially immune-mediated events.

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

Pooling of the safety data from the two pivotal trials is supported by use of the final formulation, dose, and regimen and similar safety assessment methods and duration of safety follow-up. However, the two studies differed in eligibility criteria and randomization ratio. Sci-B-Vac-001 was a smaller study with a 1:1 randomization ratio, enrolling adults across the spectrum of age groups and including subjects with well-controlled chronic diseases. Sci-B-Vac-002 was a larger trial with a 3:1 randomization ratio (Sci-B-Vac:Engerix-B), enrolling younger healthy subjects. These differences resulted in a relatively younger, healthier, and larger population who received Sci-B-Vac in the pooled safety analysis compared to the population who received Engerix-B.

8.4 Safety Results

8.4.1 Deaths

One death was reported in the pivotal clinical trials, *Sudden cardiac death*, secondary to hypertrophic heart disease, (b) (6) days post-dose 1 in Sci-B-Vac-002 (see section 6.2.12.3 for details). This death was assessed as unrelated to vaccination. No deaths were reported in the supportive trials.

8.4.2 Nonfatal Serious Adverse Events

The Applicant's SAE analysis was performed on all SAEs, including the fatal SAE. The numbers and proportions of subjects reporting at least one SAE overall during specified time periods are below.

Table 43. Number and Percentage of Subjects Reporting at Least One SAE During Select Time Periods, Integrated Summary of Safety, Safety Analysis Set

Serious Adverse Event	Sci-B-Vac N=2920 n (%)	Engerix-B N=1523 n (%)
All SAEs from Day 1-Day 28 post-vaccination	25 (0.9)	9 (0.6)
Related SAEs Day 1-Day 28 post-vaccination*	1 (0.0)	0
All SAEs from Day 1-Day 336 (end of the study)	74 (2.5)	24 (1.6)
Related SAEs from Day 1-Day 336 (end of the study)*	1 (0.0)	0

Source: Adapted from 125737/0.0, Integrated Summary of Safety, Table 23, pp. 80.
N = number of subjects with at least one documented dose; n (%) = number and percent of subjects reporting the adverse event at least once; SAE = serious adverse event
* Related was defined as very likely/certain, probably or possibly vaccine-related by the Investigator.

Reviewer comment: *Overall, the proportion of subjects reporting SAEs within 28 days following any dose and during the study is low, although a greater percentage of Sci-B-Vac recipients than Engerix-B recipients reported SAEs. This is consistent with the results of both the pivotal trials.*

Within 28 days after the last dose, 0.9% of Sci-B-Vac recipients and 0.6% of Engerix-B recipients in the pooled analysis reported SAEs. By SOC, the most frequently reported SAEs in the Sci-B-Vac group were *Infections and infestations* (Sci-B-Vac n=7, 0.2%; Engerix-B n=0), *Injury, poisoning, and procedural complications* (Sci-B-Vac n=4, 0.1%; Engerix-B n=1, 0.1%), *Hepatobiliary disorders* (Sci-B-Vac n=3, 0.1%; Engerix-B n=1, 0.1%), and *Ear and labyrinth disorders* (Sci-B-Vac n=3, 0.1% Engerix-B n=0). Three PTs were reported as SAEs within 28 days of vaccination by more than one subject in the Sci-B-Vac group, each by two subjects who received Sci-B-Vac and no subjects who received Engerix-B: *Appendicitis*, *Joint dislocation*, and *Vertigo*. No PTs were reported as SAEs within 28 days of vaccination by more than one subject in the Engerix-B group.

In the pooled analysis, from the first dose up to Day 336, SAEs were reported by 2.5% and 1.6% of subjects who received Sci-B-Vac and Engerix-B, respectively. By SOC, the most frequently reported SAEs in the Sci-B-Vac group were *Infections and infestations* (Sci-B-Vac n=20, 0.7%; Engerix-B n=3, 0.2%) and *Injury, poisoning, and procedural complications* (Sci-B-Vac n=14, 0.5%; Engerix-B n=4, 0.3%). By PT, the most frequently reported SAEs in the Sci-B-Vac group were *Appendicitis* (Sci-B-Vac n=4, 0.1%; Engerix-B n=0) and *Intervertebral disc protrusion* (Sci-B-Vac n=3, 0.1%; Engerix-B n=0). By PT, the most frequently reported SAE in the Engerix-B group were *Atrial fibrillation* (Sci-B-Vac n=1, 0.0%; Engerix-B n=2, 0.1%) and *Colon cancer* (Sci-B-Vac n=0; Engerix-B n=2, 0.1%). The following additional PTs were reported in more than one subject in the Sci-B-Vac group (2 subjects each): *Ankle fracture*, *Back pain*, *Cardiac failure congestive*, *Erysipelas*, *Joint dislocation*, *Pneumonia*, *Syncope*, *Tendon rupture*, and *Vertigo*.

Reviewer comment: *There was an imbalance noted in SAEs in the SOC of* Infections and infestations *with more subjects who received Sci-B-Vac reporting such SAEs. These SAEs represented a variety of pathogens and sites of infection and the timing and type of event did not suggest a causal relationship with vaccination. MAAEs, including serious and non-serious MAAEs, during the entire study period in the SOC of* Infections and infestations *were balanced (10.3% Sci-B-Vac; 10.0% Engerix-B).*

With regard to the four SAEs of Appendicitis*, all reported in the Sci-B-Vac group, three of the four occurred in men 41-42 YOA enrolled in Sci-B-Vac-002. The fourth was reported in a 57-year-old woman in Sci-B-Vac-001. The timing of onset following the*

subject's most recent vaccination was 4 days, 27 days, 58 days, and 110 days (the case in Sci-B-Vac-001). All of the Appendicitis *SAEs occurred in Finland, which is reported to have an annual incidence of appendicitis of 112-149/100,000 from 1990-2014; in the same study, the incidence in the US was reported as 82-111/100,000 (Ferris, 2017). The incidence of 4 in 2,920 subjects (137/100,000) in the Sci-B-Vac group over almost 1 year of observation is similar to the reported incidences. An SAE of gastrointestinal infection with abscess (no location specified) in association with gastrointestinal hemorrhage was reported in the Engerix-B group.*

One SAE was assessed as probably related to vaccination, *Gastroenteritis viral*, reported 5 days following dose 2 of Sci-B-Vac (see section 6.1.12.4 for details).

A reviewer conducted analysis by SMQ showed that SAEs in the sub-SMQ for *Vestibular disorders* were reported in 4 subjects (0.1%) in the Sci-B-Vac group and 0 subjects in the Engerix-B group. PTs reported in this SMQ were *Vertigo* (2 subjects), *Vertigo positional*, and *Vestibular neuronitis*. Three events were reported within 1 week of dose 3 of Sci-B-Vac; the fourth event, *Vestibular neuronitis*, was reported 123 days following dose 3. With regard to the events occurring within a week of vaccination, one was diagnosed as benign positional vertigo, reported 1 day following dose 3. Another event was reported in an 18-year-old woman with an elevated WBC 4 days after dose 3, who was treated with steroids and discontinuation of oral contraceptives leading to resolution in 3 weeks. The last SAE was reported in a 65-year-old woman with a past history of transient ischemic attack and cardiac myxoma and ongoing Reynaud's phenomena, who reported vertigo and transient left hand numbness 5 days after dose 3; no treatment is reported and the event resolved after 3 days. None of the events were assessed by investigators as related and all subjects fully recovered within 3 weeks.

Reviewer comment: *Although no diagnoses are reported for two of the events, the three SAEs of vertigo reported with close temporal relationship to vaccination appear to represent different etiologies given their associated signs and symptoms, time course, and treatment. Unsolicited AEs of* Dizziness *within several days of vaccination were reported more frequently following Sci-B-Vac than Engerix-B in the pooled analysis (see section 8.4.4), primarily due to a difference in Sci-B-Vac-002. Additional non-serious events of vertigo are reported in both vaccine groups in close proximity with vaccination (Days 1-3).*

8.4.3 Study Dropouts/Discontinuations

The proportions of subject who discontinued treatment due to an SAE (Sci-B-Vac n=4, 0.1%; Engerix-B n=3, 0.2%) or non-serious AE (Sci-B-Vac n=13, 0.4%; Engerix-B n=4, 0.3%) were similar between vaccine groups. Please see the individual studies, sections 6.1.12.7 and 6.2.12.7 for details.

8.4.4 Common Adverse Events

Unsolicited AEs within 28 days of any dose

The table below displays the number and proportions of subjects in the Safety Set of the pooled analysis who reported unsolicited AEs (serious and non-serious) within the 28-day post-vaccination period.

Table 44. Subjects Reporting at Least One Unsolicited AE (Serious and Non-Serious) Within the 28-Day (Days 1-28) Post-Vaccination Period, ISS, Safety Set

Adverse Event	Sci-B-Vac N=2920 n (%)	Engerix-B N=1523 n (%)
All unsolicited AEs	1411 (48.3)	737 (48.4)
Related unsolicited AE*	444 (15.2)	197 (12.9)

Source: Adapted from 125737/0.0, Integrated Summary of Safety (ISS), Table 20, pp. 67-69 and ISS – Tables, Table 3.2.2.4, pp. 2081 – 2117.
N = number of subjects with at least one documented dose; n (%) = number percent of subjects reporting the adverse event at least once; AE = adverse event
* Related was defined as very likely/certain, probably or possibly vaccine-related by the Investigator.

Reviewer comment: *In the pooled analysis, the rates of unsolicited AEs within 28 days were similar between groups, with proportionally slightly more AEs assessed as related in the Sci-B-Vac group.*

Within 28 days of any dose, the most frequently reported unsolicited AEs in the Sci-B-Vac group in the pooled analysis by PT were *Headache* (11.0% Sci-B-Vac; 10.0% Engerix-B), *Upper respiratory tract infection* (8.4% Sci-B-Vac; 7.6% Engerix-B), *Nasopharyngitis* (4.6% Sci-B-Vac; 4.8% Engerix-B), Fatigue (3.9% Sci-B-Vac; 3.7% Engerix-B), *Dysmenorrhea* (3.2% Sci-B-Vac; 2.4% Engerix-B), *Back pain* (3.1% Sci-B-Vac; 2.6% Engerix-B), *Myalgia* (2.9% Sci-B-Vac; 3.4% Engerix-B), *Oropharyngeal pain* (2.7% Sci-B-Vac; 2.6% Engerix-B), and *Injection site pain* (2.4% Sci-B-Vac; 1.6% Engerix-B). The most frequently reported (>2%) unsolicited AEs within 28 days of vaccination in the Engerix-B group are all listed above. By SOC, within 28 days of vaccination, the most frequently reported unsolicited AEs in both groups were in the SOCs of *Infections and infestations* (20.8% Sci-B-Vac; 20.9% Engerix-B), *Nervous system disorders* (13.6% Sci-B-Vac; 12.3% Engerix-B), and *Musculoskeletal and connective tissue disorders* (11.0% Sci-B-Vac; 12.1% Engerix-B). Unsolicited AEs in the SOC of *General disorders and administration site conditions* were reported more frequently in the Sci-B-Vac group (9.7%) compared to the Engerix-B group (7.8%), primarily attributable to injection site reactions.

Reviewer comment: *By PT, the most frequently reported unsolicited AEs within 28 days of vaccination were similar between groups, with* Injection site pain *being the only common unsolicited AE reported at a rate of 1.5 times greater in the Sci-B-Vac group compared to the Engerix-B group. Four of the most frequently occurring unsolicited AEs were also solicited AEs. When excluding unsolicited AEs that were solicited and lasted beyond the 7-day assessment period,* Headache *was still the most commonly reported unsolicited AE in the Sci-B-Vac group with 9.5% reporting this unsolicited AE compared to 8.0% in the Engerix-B group. The reporting rate of* Headache *starting Day 7-28 post-vaccination was similar between groups, indicating a majority of the imbalance comes in the first week post-vaccination.*

Of note, although SAEs in the SOC of Infections and Infestations *were reported more frequently during the entire study period in the Sci-B-Vac group compared to the Engerix-B group, unsolicited AEs within 28 days of vaccination in this SOC were reported at similar frequencies between groups. However, in the pooled analysis, within this SOC, some between-group differences were observed, including* Pneumonia *(Sci-B-Vac n=6, 0.2%; Engerix-B n=0) and* Vulvovaginal candidiasis *or* Vulvovaginal mycotic infection *(Sci-B-Vac n=15, 0.5%; Engerix-B n=1, 0.1%). All the AEs of* Pneumonia *were reported in subjects 46 YOA or younger; one was serious, though it did not require a*

hospitalization, and 4 of the 6 were reported 19 days or more following vaccination. Within 28 days of vaccination, the PT of Lower respiratory tract infection *was also reported exclusively in subjects who received Sci-B-Vac (n=4, 0.1%), though the* Lower Respiratory Tract Infections *HLT, which also includes* Bronchitis*, was more balanced (Sci-B-Vac 0.7%; Engerix-B 0.5%). The clinical significance of the numerical imbalance in pneumonia or vaginal fungal infections is unclear.*

In a reviewer-generated analysis by narrow SMQ, small numerical imbalances in unsolicited AEs within 28 days of vaccination in the pooled analysis were noted in the following SMQs or sub-SMQs: *Hemorrhages* (Sci-B-Vac n=66, 2.3%; Engerix-B n=24, 1.6%), including *Injection site bruising and epistaxis*; *Oropharyngeal disorders, excluding neoplasms, infections, and allergies* (Sci-B-Vac n=95, 3.3%; Engerix-B n=41, 2.7%), *Tendinopathies and ligament disorders* (Sci-B-Vac n=35, 1.2%; Engerix-B n=10, 0.7%), and *Angioedema* (Sci-B-Vac n=16, 0.5%; Engerix-B n=4, 0.3%).

Reviewer comment: *An imbalance in* Tendinopathies and ligament disorders *with more subjects in the Sci-B-Vac group reporting unsolicited AEs within 28 days of vaccination was observed in both studies. However, the proportion of subjects reporting tendinopathies was small and the reviewer is unaware of a biologically plausible mechanism.* Oropharyngeal disorders *excluding "sore throat" included several PTs such as oral numbness, tingling, or itching and oral ulcers that were reported more frequently in the Sci-B-Vac group compared to the Engerix-B group. Please see the discussion of allergy below.*

Grade 3 or greater, non-serious, unsolicited AEs within the 28-day post-vaccination period were reported by 171 subjects (5.9%) in the Sci-B-Vac group and 87 subjects (5.7%) in the Engerix-B group in the pooled analysis. The most frequently reported non-serious, Grade 3 or greater, unsolicited AEs reported within 28 days of vaccination by PT in both groups were *Headache* (Sci-B-Vac n=15, 0.5%; Engerix-B n=6, 0.4%), *Fatigue* (Sci-B-Vac n=13, 0.4%; Engerix-B n=7, 0.5%), *Back pain* (Sci-B-Vac n=11, 0.4%; Engerix-B n=6, 0.4%), and *Upper respiratory tract infection* (Sci-B-Vac n=10, 0.3%; Engerix-B n=12, 0.8%).

Unsolicited AEs occurring within 28 days following any dose that were assessed as related to vaccination by investigators were reported in 15.2% of subjects in the Sci-B-Vac group and 12.9% of subjects in the Engerix-B group in the pooled analysis. The most frequently reported PTs in both groups were also solicited AEs (*Fatigue*, *Injection site pain*, *Headache*, and *Myalgia*). In a reviewer generated analysis, when excluding unsolicited AEs categorized as reactogenicity (solicited AEs that lasted beyond the 7-day assessment period), the most frequently reported unsolicited AEs that were assessed as vaccine related were *Dizziness* (Sci-B-Vac n=29, 1.0%; Engerix-B n=8, 0.6%), *Upper respiratory tract infection* (Sci-B-Vac n=29, 1.0%; Engerix-B n=11, 0.7%), *Injection site bruising* (Sci-B-Vac n=24, 0.8%; Engerix-B n=9, 0.5%), *Oropharyngeal pain* (Sci-B-Vac n=21, 0.7%; Engerix-B n=7, 0.5%), *Nasopharyngitis* (Sci-B-Vac n=17, 0.6%; Engerix-B n=6, 0.4%), *Headache* (Sci-B-Vac n=16, 0.5%; Engerix-B n=10, 0.7%), *Abdominal pain upper* (Sci-B-Vac n=12, 0.4%; Engerix-B n=8, 0.5%), and *Back pain* (Sci-B-Vac n=11, 0.4%; Engerix-B=2, 0.1%). In labeling negotiations, the Applicant identified the following unsolicited AEs following Sci-B-Vac, for which available information suggests a causal relationship to vaccination and which will be included in the package insert: injection site bruising (1.4%, including PTs of *IS bruising*, *IS hemorrhage*, *IS hematoma*, and *Vaccination site hematoma*), dizziness/vertigo (1.1%,

including PTs *Dizziness*, *Vertigo*, and *Balance disorder*), pruritus (0.2%, including *Pruritus* and *Pruritus generalized*), *Arthralgia* (0.2%), *Urticaria* (0.2%) and *Lymphadenopathy*/*Lymph node pain* (0.1%).

Reviewer comment: *Related* Dizziness *and* Back pain *were reported at slightly higher frequencies in the Sci-B-Vac group compared to the Engerix-B group but were reported at low frequencies in both groups. CBER agreed with the inclusion of the above specified events in the prescribing information based on investigator and Applicant assessment of relationship to vaccination.*

Two subjects were identified by investigators as having an allergic reaction to vaccination based on verbatim terms reported in the datasets. Brief narratives follow.

- A 40-year-old woman with asthma (since 1994) and seasonal allergy to pollen who was treated with Symbicort (inhaled corticosteroid/long-acting bronchodilator) twice daily since 1994 was enrolled in Sci-B-Vac-002 and received three doses of Sci-B-Vac Lot B. On the day of the first dose, she reported Rhinitis (assessed as possibly related to vaccination) for 14 days, but also reported Hand, foot, and mouth disease starting 7 days post-vaccination. Following administration of the third dose, the subject experienced a non-serious AE reported by the investigator as "allergic reaction after vaccination," which included the following symptoms (verbatim terms): stuffy nose, lip itching, mouth tingling, eyelid swelling and slow vision focusing. The AEs were medically attended as it extended the vaccination study visit. The investigator assessed severity of the events as moderate (Grade 2) and very likely/certainly related to the study vaccine. She was treated with oral antihistamines (desloratadine 5 mg and loratadine 10 mg), Symbicort, and ibuprofen. Pre- and post-vaccination vital signs at this visit were reported in the datasets as stable, including a post-vaccination blood pressure that showed mild diastolic hypertension (123/93), heart rate of 66 beats per minute, and respiratory rate of 12 breaths per minute. All of the symptoms of the allergic reaction were resolved the following day.

  Reviewer comment: *This event was erroneously coded by the Applicant as "*Vaccination site hypersensitivity*." The investigator reported both the independent symptoms of the reaction, as well as his or her overall diagnosis "allergic reaction." A PT relating to respiratory distress is not reported, although the subject received her Symbicort, which would not be an appropriate treatment for anaphylaxis. If the PT of eyelid swelling were angioedema and if the subject reported difficulty breathing (leading to inhaler use), this would qualify as a level 2 Anaphylaxis, based on Brighton Collaboration criteria. The investigator did not assess this as such and given the available information, there is not enough information to meet the case definition.*

- A 49-year-old man with obesity, sleep apnea, headache, and allergy to penicillin and iodine and was enrolled in the Sci-B-Vac-001 study and received one dose of Sci-B-Vac. On the day of vaccination, he reported the following non-serious AEs (verbatim terms): feeling of heaviness in both eyes, feeling numb from the mouth, and headache (solicited AE). The investigator assessed the PTs of *Asthenopia* and *Hypoaesthesia oral* as mild and very likely/certainly related to the study vaccine. Headache was reported as moderate and related to vaccination as it was a solicited AE. None of AEs were medically attended. The subject took ibuprofen. The AEs resolved 1 day after the onset of symptoms. No further doses

of Sci-B-Vac were administered, and the investigator reported the reason for early discontinuation of the study vaccine as "Allergic reaction following the first vaccine dose". The subject continued to be evaluated for safety on study and completed the study as planned.

In response to a CBER request to summarize the allergic reactions to Sci-B-Vac, the Applicant conducted an analysis to identify any other AEs which may be considered potential allergic reactions to Sci-B-Vac. They considered all reported AEs in the SMQs for *Anaphylactic reaction* and *Hypersensitivity*. The Applicant's search identified 47 AEs in Sci-B-Vac group and 49 AEs in the Engerix-B group in Sci-B-Vac-001 and 51 AEs in Sci-B-Vac Lot A, 46 AEs in Sci-B-Vac Lot B, 44 AEs in Sci-B-Vac Lot C, and 45 AEs in Engerix-B group in Sci-B-Vac-002. Please see the table below for the reviewer's search of the same SMQs Days 1-7 following any dose.

Table 45. Reviewer-Generated Analysis of the Number and Percentage of Subjects and Terms in Narrow SMQs Potentially Signifying Allergic Reactions Days 1 Through 7 Following Any Vaccine Dose, ISS, Safety Analysis Set

Narrow SMQ	Sci-B-Vac N=2920 Number of AEs/Number of Subjects (%)	Engerix-B N=1523 Number of AEs/Number of Subjects (%)
Anaphylactic reaction	0	0
Hypersensitivity	40/36 (1.2)	12/12 (0.8)

Source: Reviewer-generated analysis from integrated safety datasets ADSL and ADAE.
N = number of subjects with at least one documented dose; n (%) = number percent of subjects reporting the adverse event at least once

The Applicant reviewed the clinical features of all the AEs they identified by the SMQ search, including the verbatim and PTs, affected area (e.g., beyond the injection site or generalized), timing of AEs relative to study vaccination (e.g. within 1-7 days), investigators' assessment of causality and severity, actions taken (e.g., vaccine withdrawal), whether the AEs were medically attended or required treatment, and whether the AEs recurred after subsequent vaccine dose(s) were administered." The Applicant provided narratives for each of these events. The below table summarizes the PTs and key features of the potential vaccine hypersensitivity events identified by the Applicant. PTs and subject numbers were also provided for Engerix-B subjects identified through the same process.

Table 46. Potential Allergic Reactions Identified by the Applicant Following Sci-B-Vac and Engerix-B, Safety Analysis Set

Vaccine Group	Study	Age (years) / Sex	PT/Verbatim	Day of Onset/ Post-dose Number	Duration (days)	Severity	Related per Investigator	Treatment	Revaccinated	Notes
Sci-B-Vac	-001	69/F	Rash/ Systemic rash	3 / 1	3	Mild	Probable	No	Yes, 2 doses, no recurrence	
Sci-B-Vac	-001	67/F	Urticaria/ Urticaria	3 / 1	13	Moderate	Unlikely	Diphenhydramine, Methylprednisone, Doxycycline	Yes, 2 doses, no recurrence	Medically attended, Diphenhydramine taken post-dose 2 but no AE reported, history of codeine allergy
Sci-B-Vac	-001	35/F	Urticaria/ Worsening of urticaria	1 / 1	1	Mild	Probable	No	Yes, 2 doses, no recurrence	10-year history of intermittent urticaria
Sci-B-Vac Lot A	-002	42/F	Pruritus generalized/ Itchiness all over body	0 / 2	15	Mild	Very likely/ certain	No	Yes, 1 dose, no recurrence	History of nitrofurantoin allergy
Sci-B-Vac Lot C	-002	31/F	1) Urticaria 2) Urticaria/ Urticaria right upper arm	1) 1 / 1 2) 1 / 2	1) 1 2) 1	3) Mild 4) Mild	1) Possible 2) Possible	No	Yes, recurred post-dose 2, no recurrence post-dose 3	
Sci-B-Vac Lot B	-002	28/F	Urticaria/ Urticaria in shoulders	2 / 1	3	Mild	Possible	No	Yes, no recurrence	
Sci-B-Vac Lot B	-002	41/M	Rash on forearms	0 / 3	3	Moderate	Possible	No	No	
Sci-B-Vac Lot B	-002	24/M	Urticaria	1 / 3	17	Severe	Probable	No	No	
Sci-B-Vac Lot B	-002	36/F	Pruritus generalized/ Itchiness all over the body	2 / 3	16	Moderate	Possible	Desloratadine 3 days, hydrocortisone topical 1 day	No	History of pollen allergy
Sci-B-Vac Lot A	-002	35/F	Urticaria/ Urticaria	2 / 1	1	Moderate	Possible	No	Yes, no recurrence	

Vaccine Group	Study	Age (years) / Sex	PT/Verbatim	Day of Onset/ Post-dose Number	Duration (days)	Severity	Related per Investigator	Treatment	Revaccinated	Notes
Sci-B-Vac Lot A	-002	34/M	Pruritus generalized/ Total body itch Swelling face/ Face swelling	3 / 3	3	Severe	Possible	Levocetirizine and cetirizine	No	Medically attended
Engerix-B	-001	66/F	Angioedema/ Angio/edema	7 / 2	8	Severe	Unlikely	Cortisone IV, cortisone, hydrocortisone (snake bite package), certirizine	Yes, one dose, no recurrence, eczema post-dose 3	Medically attended ER visit
Engerix-B	-002	20/F	Urticaria/ Urticaria in legs and back	1 / 3	1	Moderate	Possible	Certirizine, hydrocortisone topical, ibuprofen	No	History of food allergy
Engerix-B	-002	35/F	Lip swelling/ Swollen lower lip	2 / 2	4	Mild	Possible	No	Yes, one dose, no recurrence	Concurrent Lip blister/ Lip vesicle reported, history of food and seasonal allergy
Engerix-B	-002	36/F	Dermatitis allergic/ Allergic rash on the arms	5 / 1	11	Moderate	Unlikely	Hydrocortisone topical, ebastine (antihistamine)	Yes, two doses, no recurrence	History of dog allergy
Engerix-B	-002	28/F	Rash/ Rash in Upper Trunk	0 / 2	5	Mild	Possible	Hydrocortisone topical	Yes, one dose, no recurrence	History of urticaria, milk allergy, allergic rhinitis
Engerix-B	-002	32/F	Rash generalized/ Rash on the body	0 / 1	5	Moderate	Possible	No	Yes, two doses, no recurrence	History of pollen allergy

Source: Reviewer-generated table based on the summary of possible allergic reactions provided in 125737/0.19 and 125737/0 25, Clinical Information Amendments.
Day of onset is the number of days after vaccination. Day 0 is the day of vaccination. Events were not medically attended unless noted otherwise.
PT = preferred term; F = female; M = male; AE = adverse event

In total, including the events identified as allergic reactions by investigators (described above the table), the Applicant identified 13 subjects (0.4%) in the Sci-B-Vac group and 6 (0.4%) subjects in the Engerix-B group who reported events that are potential allergic reactions. Of these events, 12 subjects (0.4%) in the Sci-B-Vac group and 4 subjects (0.3%) in the Engerix-B group reported an event that was assessed as vaccine-related. Seven subjects in the Sci-B-Vac group and 5 subjects in the Engerix-B group did not report recurrence of symptoms following administration of any subsequent dose(s) of vaccine. Most events were not medically attended. Two subjects (0.1%) in the Sci-B-Vac group and 0 subjects in the Engerix-B group had medically attended potentially allergic events that were assessed as related. One event in the Sci-B-Vac group was medically attended, assessed as severe and related – *Pruritus generalized* and *Swelling face*.

In addition to the two events in the Sci-B-Vac group, considered allergic reactions by the investigators, the reviewer identified 3 subjects (0.1%) in the Sci-B-Vac group and no subjects in the Engerix-B group, who reported oral paresthesia, hypoesthesia, or pruritus. All events were mild. One subject reported *Hypoesthesia oral* that occurred following dose 1 and 2 and was assessed by the investigator as vaccine-related; the other two events were assessed as unlikely to be related to vaccination.

Reviewer comment: *Several events were identified that may represent a vaccine hypersensitivity. In the pivotal trials, there were no serious events and no clear report of anaphylaxis following vaccination. Two investigator-assessed allergic reactions similar to the above-described events were identified in the supportive trials (see section 9.2); one was assessed as serious due to medical significance (no hospitalization) and the other mild event (rash and lymphadenopathy) led to discontinuation. Most of the hypersensitivity events were mild to moderate, did not require medical attention, and did not recur with subsequent doses. Events were reported in both vaccine groups in roughly similar proportions, although a small increase in non-serious vaccine-related hypersensitivity in the Sci-B-Vac group can't be ruled out.*

Medically attended adverse events

The table below displays the number and proportions of subjects in the Safety Set of the pooled analysis who reported MAAEs (serious and non-serious) within the specified time windows.

Table 47. Subjects Reporting at Least One Medically Attended Adverse Event (Serious and Non-Serious) Within the 28-day (Days 1 to 28) Post-Vaccination Period and the Entire Study (Days 1 to 336), ISS, Safety Set

Adverse Event	Sci-B-Vac N=2920 n (%)	Engerix-B N=1523 n (%)
MAAEs Day 1-28 following any dose	397 (13.6)	225 (14.8)
Related MAAE Day 1-28 following any dose*	23 (0.8)	7 (0.5)
MAAEs Day 1-336	663 (22.7)	356 (23.4)
Related MAAEs Day 1-336	24 (0.8)	8 (0.5)

Source: Adapted from 125737/0.0, Integrated Summary of Safety, Table 20, pp. 67-69 and Table 3.2.2.13a and reviewer generated analysis from Integrated Summary of Safety ADSL and ADAE datasets.
N = number of subjects with at least one documented dose; n (%) = number and percent of subjects reporting the adverse event at least once; MAAE = medically attended adverse event
* Reviewer generated analysis

Reviewer comment: *In the pooled analysis, the rates of MAAEs within 28 days and during the entire study were similar between groups.*

Within 28 days of any dose, the most frequently reported MAAEs in the Sci-B-Vac group in the pooled analysis by PT were *Upper respiratory tract infection* (Sci-B-Vac n=31, 1.1% Sci-B-Vac; Engerix-B n=16, 1.1%), *Urinary tract infection* (Sci-B-Vac n=21, 0.7%; Engerix-B n=18, 1.2%), *Sinusitis* (Sci-B-Vac n=21, 0.7%; Engerix-B n=12, 0.8%), and *Back pain* (Sci-B-Vac n=15, 0.5%; n=6, 0.4%). Within 28 days of any dose, the most frequently reported MAAEs assessed by investigators as related in the Sci-B-Vac group were *Upper respiratory tract infection* (Sci-B-Vac n=4, 0.1%; Engerix-B n=0) and *Dizziness* (Sci-B-Vac n=2, 0.1%; Engerix-B n=0).

During the entire study, Day 1 through 336, the most common MAAEs in the Sci-B-Vac group were *Upper respiratory tract infection* (Sci-B-Vac n=43, 1.5%; Engerix-B n=20, 1.3%), *Sinusitis* (Sci-B-Vac n=39, 1.3%; Engerix-B n=18, 1.2%), *Urinary tract infection* (Sci-B-Vac n=36, 1.2%; Engerix-B n=25, 1.6%) and *Back pain* (Sci-B-Vac n=25, 0.9%; Engerix-B n=7, 0.5%). The additional MAAEs assessed as related that occurred beyond Day 28 post-vaccination were *Urinary tract infection* 127 days following Sci-B-Vac dose and *Arthralgia* 115 days following Engerix-B dose.

New-onset chronic illnesses

This summary of NOCIs is reviewer generated and includes both AEs collected and identified by the investigator as NOCIs and those identified by the MM based on the CDC listing of chronic diseases from vaccination to Day 336. The Applicant presented NOCIs identified by the investigator and MM separately.

The total number (percentage) of investigator and MM identified NOCIs was 64 (2.2%) in the Sci-B-Vac group and 41 (2.7%) in the Engerix-B group. By PT, the most frequently reported NOCIs in the Sci-B-Vac group were *Hypertension* (Sci-B-Vac n=9, 0.3%; Engerix-B n=7, 0.5%), *Hypothyroidism* (Sci-B-Vac n=4. 0.1%; Engerix-B n=6, 0.4%), *Type 2 diabetes mellitus* (Sci-B-Vac n=3, 0.1%; Engerix-B n=0), and *Depression* (Sci-B-Vac n=3, 0.1%; Engerix-B n=0). No NOCIs in the Sci-B-Vac group were assessed as related by investigators, other than two reactogenicity events that appear to be incorrectly categorized as NOCIs (see section 6.1.12.2).

Reviewer comment: *No clinically significant imbalances were observed in NOCIs. The reviewer performed an analysis of all treatment emergent AEs reported in subjects in the pooled Safety Analysis Set to evaluate AEs with PTs in the SMQ for Immune-mediated/Autoimmune Disorders. The ADAE dataset was used and all AEs were included (unsolicited AEs, MAAEs, NOCIs, SAEs, AEs leading to withdrawal) regardless of protocol specified assessment periods. MedDRA version 23.1 was used as the earliest version with this SMQ. This analysis identified three subjects in each vaccine group with such events reported (0.1% Sci-B-Vac; 0.2% Engerix-B). These events, with PTs of* Rheumatoid arthritis *(n=2) and* Sarcoidosis *in the Sci-B-Vac group and* Polymyalgia rheumatica *(n=2) and* Chronic gastritis *in the Engerix-B group, are discussed in sections 6.1.12.2 and 6.2.12.2.*

8.4.5 Clinical Test Results

Please see the descriptions of clinical test results of the individual pivotal trials in 6.1.12.6 and 6.2.12.6.

8.4.6 Systemic Adverse Events

Please see the descriptions of solicited systemic AEs of the individual pivotal trials in 6.1.12.2 and 6.2.12.2.

8.4.7 Local Reactogenicity

Please see the descriptions of solicited local AEs of the individual pivotal trials in 6.1.12.2 and 6.2.12.2.

8.4.8 Adverse Events of Special Interest

Not applicable.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

The pooled analysis evaluated a single dose level. Solicited AEs did not generally increase with increasing dose number (see sections 6.1.12.2 and 6.2.12.2).

8.5.2 Time Dependency for Adverse Events

See sections 6.1.12.2 and 6.2.12.2 for details on the duration of common (solicited) AEs.

8.5.3 Product-Demographic Interactions

The studies were not powered to evaluate differences in safety based on demographic groupings, so the clinical significance of any differences noted between groups in the below analyses is unknown. Please see the demographic distribution in the integrated safety population in section 8.2.2.

Serious adverse events: From Day 1-336, in the overall study population, SAEs were reported more frequently in the Sci-B-Vac compared to Engerix-B group (2.5% Sci-B-Vac; 1.6% Engerix-B). By age, SAEs were reported more frequently in the Sci-B-Vac group in the youngest (18-44 YOA: 2.1% Sci-B-Vac; 0.4% Engerix-B) and oldest age groups (≥65 YOA: 4.7% Sci-B-Vac; 2.4% Engerix-B). SAEs were reported at similar frequencies between groups in the 45-64 YOA age group (3.5% Sci-B-Vac; 3.7% Engerix-B). The overall incidence of SAEs increased with increasing age in the Sci-B-Vac group (18-44 YOA: 2.1%, 45-64 YOA: 3.5%, ≥65 YOA: 4.7%), whereas in the Engerix-B group, the incidence of SAEs was highest in subjects 45-64 YOA: (18-44 YOA: 0.4%, 45-64 YOA: 3.7%, ≥65 YOA: 2.4%).

Reviewer comment: *SAEs in the Sci-B-Vac group follow an expected pattern of increasing rate with increasing age. There was no pattern in type or timing of SAE to indicate a risk of SAEs following vaccination in any age group.*

As in the overall ISS, SAEs were reported more frequently in the Sci-B-Vac group compared to the Engerix-B group in women (2.7% Sci-B-Vac; 1.5% Engerix-B) and men (2.4% Sci-B-Vac; 1.7% Engerix-B). There were no clinically significant differences in SAEs in the Sci-B-Vac group by gender. In White subjects, as in the study overall, subjects in the Sci-B-Vac group reported more SAEs than subjects in the Engerix-B group (2.6% Sci-B-Vac; 1.5% Engerix-B). In Black or African American subjects, SAEs were more frequent in the Engerix-B group (3 subjects, 1.6% Sci-B-Vac; 3 subjects,

2.9% Engerix-B), but were reported in few subjects overall. Only one SAE was reported in the other race group and none in the Asian race group. In non-Hispanic or Latino subjects, as in the study overall, subjects in the Sci-B-Vac group reported SAEs more frequently than subjects in the Engerix-B group (2.7% Sci-B-Vac; 1.5% Engerix-B). In Hispanic or Latino subjects, SAEs were reported at similar frequencies between groups (3 subjects, 1.1% Sci-B-Vac; 2 subjects, 1.3% Engerix-B), but were reported in few subjects overall.

Reviewer comment: *Differences in SAE frequency by demographic subgroups generally reflected the differences noted in the overall pooled population, particularly for the largest demographic subgroups. No differences likely to be clinically significant were noted by subgroup.*

Unsolicited AEs reported during the 28-day post-vaccination period: Following Sci-B-Vac, the frequency of subjects reporting unsolicited AEs decreased with increasing age group (18-44 YOA: 50.1%, 45-64 YOA: 45.8%, ≥65 YOA: 38.9%). In all age groups the proportion of subjects reporting unsolicited AEs following Sci-B-Vac was similar to or lower than following Engerix-B. Events in the *Musculoskeletal and connective tissue disorders* SOC, in particular back pain and arthralgia, were reported more frequently in the 45-64 YOA group following Sci-B-Vac (14.4%) compared to Engerix-B (10.7%), a between-group difference which was not observed in other age groups. In the Sci-B-Vac group, females reported AEs at a higher rate than males (54.5% and 39.8%, respectively), but rates were similar between vaccine groups by gender. In the Sci-B-Vac group the proportions of subjects reporting unsolicited AEs (serious and non-serious) during the 30-day post-vaccination period by race ranged from 31.1% (Asian race) to 50.0% (Other race). By race, the proportions of subjects reporting unsolicited AEs were similar between vaccine groups, with the exception of other races (50.0% Sci-B-Vac; 39.1% Engerix-B), which was the smallest race group with 53 subjects in the pooled safety population. The proportion of non-Hispanic or Latino subjects (50.2%) reporting unsolicited AEs within 28 days of Sci-B-Vac vaccination was higher than that in the Hispanic or Latino group (31.4%), but between vaccine groups unsolicited AEs were reported at similar frequencies.

Reviewer comment: *As musculoskeletal and connective tissue disorders, including back pain and arthralgia, were reported more frequently in the Engerix-B group compared to the Sci-B-Vac group in subjects ≥65 YOA, and at similar rates between vaccine groups in subjects 18-44 YOA, the difference observed in the 45-64 YOA group may have been by chance.*

Solicited AEs during the 7-day post-vaccination period: Rates of solicited local and systemic AEs following Sci-B-Vac were similar in 18-44 YOA subjects enrolled in Sci-B-Vac-001 and in subjects enrolled in Sci-B-Vac-002, with the exception that *Headache* was reported more frequently (51.0%) in subjects 18-44 YOA in Sci-B-Vac-001 than in subjects in Sci-B-Vac-002 (38.2%). Please see section 6.1.12.2 for a presentation of solicited AEs by age group. In general, among Sci-B-Vac recipients, the incidence of solicited local and general symptoms decreased with increasing age, though not as notably as in Engerix-B recipients. When both Sci-B-Vac-001 and Sci-B-Vac-002 are included, the proportions of females in the Sci-B-Vac group reporting solicited local and general symptoms (86.5% and 70.8%, respectively) was higher than males (74.4% and 56.5%, respectively). By race, incidence of solicited local AEs ranged from 55.6% in Black or African American subjects to 83.3% in White subjects; incidence of solicited

systemic AEs ranged from 42.3% in Black subjects to 71.1% in Asian subjects. Hispanic or Latino subjects were less likely to report local (60.6%) and systemic (50.0%) solicited AEs following Sci-B-Vac than non-Hispanic or Latino subjects (83.5% and 66.3%, respectively). The frequencies of Grade 3 or greater local and systemic solicited AEs following Sci-B-Vac were similar between subgroups or followed the same patterns as reports of any grade local and systemic solicited AEs, with the exception that Hispanic or Latino subjects were slightly more likely to report Grade 3 or greater local (3.6%) and solicited (4.4%) AEs following Sci-B-Vac than Non-Hispanic or Latino subjects (2.8% and 2.8%, respectively).

8.6 Safety Conclusions

The two pivotal trials were pooled to identify patterns of AEs and assess for the occurrence of uncommon AEs. Pooling was supported by use of the same Sci-B-Vac formulation, dose, and regimen, and similar safety assessments and follow-up times between trials. The proportion of subjects who reported SAEs from Day 1 to 336 was higher in the Sci-B-Vac group compared to the Engerix-B group (Sci-B-Vac n=74, 2.5%; Engerix-B n=24, 1.6%), while SAEs within 28 days of any vaccination were reported at relatively similar rates between groups (Sci-B-Vac n=25, 0.9%; Engerix-B n=9, 0.6%). Four subjects in the Sci-B-Vac group reported SAEs of appendicitis with onset 4-110 days following any vaccination. These events were not clustered in time to suggest vaccine relationship. No patterns of SAE type or timing were observed to suggest a vaccine-related risk. In general, overall proportions of unsolicited AEs (serious and non-serious) were reported at similar rates in both vaccine groups, with the exception of injection site pain extending beyond the 7-day assessment period, which was reported at a slightly higher rate in the Sci-B-Vac group. In the pooled analysis, a small increase in hypersensitivity events following Sci-B-Vac compared to Engerix-B, cannot be ruled out; events were non-serious and typically mild with many not recurring following additional doses of vaccine.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Sci-B-Vac is proposed for use in women 18 YOA and older, including those of reproductive potential. The use of sci-B-Vac in pregnant or lactating women has not been prospectively studied during the development program. Pregnant and lactating women were ineligible to participate in the pivotal clinical trials, and appropriate contraceptive measures were required to avoid exposure during pregnancy.

Subjects reported 20 pregnancies during the two pivotal studies, including 4 subjects in the Sci-B-Vac-001 study (3 Sci-B-Vac, 1 Engerix-B) and 16 subjects in the Sci-B-Vac-002 study (15 Sci-B-Vac, 1 Engerix-B). The following outcomes were reported in the 18 pregnancies in the Sci-B-Vac groups in the pivotal trials:

- 2 unknown outcomes, one for which the subject's last menstrual period (LMP) is reported prior to the subject's last vaccination
- 4 elective terminations with no congenital anomalies reported by the Applicant
- 2 miscarriages, including a "fetal demise" at 14 weeks gestation with a congenital anomaly (see below)
- 10 live births at term, including one minor congenital anomaly (see below).

Reviewer comment: *When considering subjects 18-44 YOA in the integrated safety database, a greater percentage of Sci-B-Vac subjects (0.8%) compared to Engerix-B subjects (0.2%) reported a pregnancy. The reason for the imbalance is unclear. No components of this vaccine are expected to contribute to an increase in fertility. It is also possible pregnancies may have occurred beyond 4 weeks following the third dose, but not been reported per the protocol (one was reported in the Sci-B-Vac group). Seven subjects who received Sci-B-Vac and became pregnant had LMPs (or calculated start date of pregnancy if the LMP was unknown) prior to the subject's last vaccination. Each of these subjects delivered a full-term live infant.*

Brief narratives of the adverse pregnancy outcomes and congenital anomalies follow:

- A 43-year-old woman with obesity, pre-diabetes, depression, anxiety, ankle enthesopathy, and an obstetric history of five previous pregnancies (4 live births, one miscarriage) enrolled in Sci-B-Vac-001 and received two doses of Sci-B-Vac. The third dose of study vaccine was not administered due to a positive urine pregnancy test. LMP was reported as approximately 3 months following the subject's last vaccination (dose 2). Non-invasive pre-natal testing showed trisomy 21, confirmed by chorionic villus biopsy. The subject experienced vaginal bleeding with subchorionic hemorrhage to the gestational sac on Day 176. Fetal demise at approximately 14 weeks gestation due to a large subchorionic hemorrhage was diagnosed via ultrasound on Day 212, 183 days after the subject's last dose of study vaccine. A dilation and curettage were performed. The investigator assessed the SAEs of *Trisomy 21* and "fetal demise due to subchorionic hemorrhage" as unrelated to vaccination.
- A 41-year-old woman with migraines and seasonal allergies enrolled in Sci-B-Vac-002 and received two doses of Sci-B-Vac, following negative pregnancy tests immediately prior to each dose. A pregnancy test was positive 146 days after the subject's last dose and a spontaneous abortion was reported 7 days later. LMP was unknown.

  Reviewer comment: *Both spontaneous abortions (including the "fetal demise') were reported in women who were not exposed to study vaccine during pregnancy. They are, therefore, unlikely to be related to vaccination.*

- 39-year-old woman with post-traumatic stress disorder (treated with sertraline) and sciatica enrolled in Sci-B-Vac-002 and received two doses of Sci-B-Vac. The subject reported pregnancy with an LMP of approximately 2 months following the subject's last dose of study vaccine. The subject delivered a full-term live infant with no congenital anomalies noted at birth. Delivery complications are reported as maternal hemorrhage of <1 L. Following database lock an SAE (congenital anomaly) of Ankyloglossia was reported. The congenital anomaly did not require surgery and was assessed by the investigator as mild and possibly related to study vaccination, due to the temporal relationship.

  Reviewer comment: *The reviewer agrees with the Applicant that this minor congenital anomaly is not related to the study vaccine, as there was no exposure to study vaccine during pregnancy.*

Pregnancy complications or AEs included one subject who reported gestational diabetes and another subject with moderate vomiting of pregnancy; both pregnancies resulted in a healthy term infant.

The Applicant provided a summary of pregnancies reported in the Sci-B-Vac groups (all formulations) in the supportive studies. Eighteen pregnancies were reported in eighteen subjects in the Sci-B-Vac groups; the outcomes of five of these subjects' pregnancies are known:

- Two induced abortions of pregnancies estimated as occurring 1 to 4 weeks following vaccination.
- Three full-term deliveries of healthy infants without congenital anomalies noted. These pregnancies are estimated to have occurred 1) one month prior to first dose (subject also received a second dose), 2) 1 to 4 weeks following the subject's last dose, and 3) 4 months following the subject's last dose.

Reviewer comment: *The information available on pregnancies in the supportive trials is limited. Few pregnancies were reported in the pivotal trials. Of seven women who became pregnant around the time of vaccination, all delivered live term infants. Although the information is limited, no safety signals were identified. These data are insufficient to inform vaccine-associated risks in pregnancy. A pregnancy registry is planned as a postmarketing commitment.*

9.1.2 Use During Lactation

No data is available to evaluate the safety of Sci-B-Vac during lactation.

9.1.3 Pediatric Use and PREA Considerations

The Applicant requested and will receive a full waiver for assessments in all pediatric age groups. See section 5.4 for details.

9.1.4 Immunocompromised Patients

Sci-B-Vac was not evaluated in immunocompromised subjects in the pivotal or supportive trials.

9.1.5 Geriatric Use

The proposed population for use is adults 18 YOA and older. The Applicant provided analyses of immunogenicity and safety in subjects ≥65 YOA as part of subgroup analyses for study Sci-B-Vac-001 and in the ISS. Results in this age group from Sci-B-Vac-001 are presented below. No subjects over 45 YOA were enrolled in Sci-B-Vac-002.

In Sci-B-Vac-001, 592 subjects ≥65 YOA were included in the Safety Set, 296 in both the Sci-B-Vac and Engerix-B groups. Approximately 43% of these subjects were ≥70 YOA. Ten subjects in the Sci-B-Vac group and 9 subjects in the Engerix-B group were 80 YOA or older. Demographic characteristics in subjects ≥65 YOA were similar between vaccine groups and similar to the overall study population for characteristics other than age, with the exception of a greater percentage of men in both treatment groups in subjects ≥65 YOA (46%) compared to the entire study population (38%).

Efficacy: In subjects ≥65 YOA, the SPR (95% CI) was 83.6% (78.6%, 87.8%) in the Sci-B-Vac group and 64.7% (58.6%, 70.4%) in the Engerix-B group.

Reviewer comment: *Compared to the SPRs in the 18-44 YOA group [99.2% (95.6%, 100.0%) Sci-B-Vac; 91.1% (85.0%, 95.3%) Engerix-B] and the 45-64 YOA group [94.8% (91.8%, 96.9%) Sci-B-Vac; 80.1% (75.3%, 84.3%) Engerix-B], the SPRs in subjects* ≥65

YOA in both the Sci-B-Vac and Engerix-B group were lower. However, the decline in SPR with increasing age was less pronounced in the Sci-B-Vac group.

Serious adverse events: No deaths were reported in the Sci-B-Vac-001. In subjects 65 YOA and older, up to 28 days following the last dose, 6 subjects (2.0%) in the Sci-B-Vac group and 2 subjects (0.7%) in the Engerix-B group reported SAEs. Up to study Day 336, 14 subjects (4.7%) in the Sci-B-Vac group and 7 subjects (2.4%) in the Engerix-B group reported SAEs.

Reviewer comment: *The proportion of subjects ≥65 YOA reporting SAEs was numerically higher in the Sci-B-Vac group compared to the Engerix-B group. The proportion of subjects ≥65 YOA in the Engerix-B group reporting SAEs during the entire study period was lower than the proportion of subjects 45-64 YOA in the Engerix-B group reporting SAEs (3.9%), suggesting the observed SAE estimates in the ≥65 YOA Engerix-B group may be lower than expected. Furthermore, the proportions of subjects reporting SAEs in the Sci-B-Vac group increased with increasing age (18-44 years: 2.1%; 45-64 years: 3.5%; ≥65 years: 4.7%), as would be expected. The timing and nature of the SAEs reported in subjects ≥65 YOA did not suggest relationship to vaccination.*

Unsolicited AEs reported during the 28-day post-vaccination period: In subjects ≥65 YOA, up to 28 days following any dose, 38.9% of subjects in the Sci-B-Vac group and 42.9% of subjects in the Engerix-B group reported unsolicited AEs (serious and non-serious). In a reviewer-generated analysis, MAAEs in subjects ≥65 YOA were reported by 24.0% and 28.4% of subjects who received Sci-B-Vac and Engerix-B, respectively, and NOCIs in subjects ≥65 YOA were reported by 4.7% and 5.7% of subjects who received Sci-B-Vac and Engerix-B, respectively.

Reviewer comment: *More subjects in the Sci-B-Vac group reported* Pruritus *or* Pruritus generalized *(4 subjects, 1.3%) and* Oropharyngeal pain *(5 subjects, 1.7%) compared to the Engerix-B group (0 subjects and 1 subject, 0.3%, respectively). Otherwise, no clinically relevant imbalances in unsolicited AEs were noted by primary SOC or by PT between Sci-B-Vac and Engerix-B groups.*

Solicited AEs during the 7-day post-vaccination period: The proportion of subjects ≥65 YOA reporting solicited local AEs was 62.2% and 35.5% in the Sci-B-Vac and Engerix-B groups, respectively. Among Sci-B-Vac recipients, the incidence of solicited local symptoms was higher in the 18-44 (80.7%) and 45-64 YOA groups (76.3%) when compared to the ≥65 YOA group (62.2%). Among Sci-B-Vac recipients, the incidence of general symptoms was higher in 18-44 (73.1) and 45-64 YOA groups (59.7%) when compared to ≥65 YOA group (42.9%). Grade 3 local and general symptoms tended to be higher in the younger age group. Among Sci-B-Vac recipients ≥65 YOA, the most commonly reported local symptoms were pain and tenderness (53% each). Grade 3 pain or tenderness were not reported in Sci-B-Vac recipients in this age group. The most commonly reported general symptoms among Sci-B-Vac recipients ≥65 YOA were myalgia (27.4%) and fatigue (24.3%). Grade 3 myalgia or fatigue were not reported in Sci-B-Vac recipients in this age group.

Reviewer comment: *Overall, solicited AEs were reported less frequently in subjects ≥65 compared to younger subjects.*

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

The clinical development program of Sci-B-Vac includes non-IND studies conducted beginning in 1990. In pre-BLA discussions, CBER agreed that the pivotal IND studies, Sci-B-Vac-001 and Sci-B-Vac-002, were anticipated to be sufficient to assess the safety and efficacy of Sci-B-Vac in preventing hepatitis B virus infection in adults, and that other studies conducted by the Applicant during the development program would be considered supportive. At the request of CBER to facilitate a more thorough review of safety, for the non-IND studies evaluating any formulation or dose of Sci-B-Vac in adults, the Applicant submitted the following:

- protocol synopses
- subjects enrolled, including demographics and subject disposition
- methods of SAE data collection
- tabular summaries of SAEs and any other events that the Applicant considered clinically significant (for example Grade 3 adverse events)
- SAE narratives

The supportive Sci-B-Vac studies in previously unvaccinated adults included five comparative Phase 2 or 3 studies, three Phase 2 dose-finding studies, and two single-arm, open-label studies (Phase 2, Phase 4). In addition, one Phase 3 study evaluated one to two doses of Sci-B-Vac ([(b) (4)] mcg) and Engerix-B in subjects who had received prior HBV vaccination. Each of these studies evaluated immunogenicity and established rates of seroprotection based on proportion of study subjects achieving anti-HBs titers ≥10 mIU/mL. Safety evaluations included 1,881 adults who received at least one dose of the current or prior formulation of Sci-B-Vac (5-[(b) (4)] mcg HBsAg) followed for up to 1 year from the time of first dose. Studies were conducted in countries outside of the US, mostly Israel and Asian countries.

The summary reports were reviewed. Many of the submitted trials did not employ the safety monitoring or presentation of safety data that is routinely used for current IND trials. Grading criteria were sometimes not clearly presented, except for pain. Consequently, it is not possible to accurately compare severe events (such as fever) across supportive trials or within the pivotal trials. In the synopses, for non-serious unsolicited AEs, only vaccine-related AEs were reported by the Applicant. The following is a summary of pertinent points:

- The trials were generally conducted in a young population of healthy individuals. Of note, several of the trials were conducted in Asian countries, enrolling approximately 520 subjects who received Sci-B-Vac (any dose formulation).
- Almost all individuals vaccinated with Sci-Vac demonstrated an immune response and achieved a seroprotective antibody level.
- In general, injection site pain was the most commonly reported AE post-vaccination and severe injection site pain was the most commonly reported Grade 3 AE.
- In study 38-92-001, completed in 1994, two lots of prior formulations of Sci-B-Vac (Lot A and Lot B, both with 5 mcg, $AlPO_4$ and thimerosal) appear to have differing reactogenicity profiles, with increased fever (5.9%) and pain (60.7% following dose 1) in lot A compared to lot B (0% and 42.4%, respectively). One subject discontinued treatment due to rash and cervical lymphadenopathy that is reported to be a suspected allergic reaction; this event was not reported to be serious or of ≥ Grade 3 severity.

- Study HBV-002 was an open-label, randomized trial conducted in 2003 in subjects who previously received a hepatitis B vaccine and were classified as non- and low-responders to compare the immunogenicity and safety of one to two doses of (b) (4) mcg of a prior formulation of Sci-B-Vac ($Al(OH)_3$, no thimerosal) to Engerix-B (20 mcg). The following AEs were noted by the reviewer as pertinent to the current assessment of safety:
    - One non-serious AE of psoriasis aggravated was assessed as, not severe and vaccine-related. Other select non-serious vaccine-related AEs included dizziness (n=2, 0.4%, one assessed as severe), and vertigo, tinnitus, and hyperbilirubinemia (severe) in one subject each.
    - A 52 year-old woman who received Sci-B-Vac in HBV-002 reported severe pain and injection site warmth on Day 2, severe face edema on Day 3-4, and severe hives on Day 4-6. The investigator assessed the events as related, not life-threatening, and serious (medically significant). The events resolved without sequelae. It is unclear from the narrative if the events were medically attended or if the subject received treatment. The following co-medications are listed: betamethasone, ipratropium bromide, budesonide, temazepam and valproic acid.

  Reviewer comment: *This event, as well as the rash reported in 38-92-001, is similar to other hypersensitivity events occurring in the days following vaccination reported in the Sci-B-Vac pivotal trials (see section 8.4.4). The Applicant notes that the dose evaluated in HBV-002 is not the proposed dose. In addition to this event, the reviewer assessed one additional SAE in SG-005-05 (2008), which the investigator assessed as syncope or allergic reaction related to Sci-B-Vac vaccination and treated with IV steroids and IV calcium chloride, as a syncopal reaction following vaccination, a well-described reaction to vaccines in young adults.*

    - A 41-year-old woman was vaccinated with a prior formulation of Sci-B-Vac in HBV-002 and was hospitalized for an SAE of papilledema and vasculitis 2 months following vaccination, with "bulbitis" reported one month later. She was treated with diclofenac, prednisolone and acetazolamide. No diagnosis is provided. The investigator assessed the event as unrelated to vaccination. The Applicant was queried regarding this event at the time of the pre-IND and had no additional information regarding an overarching diagnosis.

  Reviewer comment: *No similar events are reported in the pivotal trials.*

- As per the study synopsis of HBV-003-89 (completed in 1993), a trial comparing two doses of a prior formulation of Sci-B-Vac, "In March 1991, a cluster of symptoms including headache, dizziness, asthenia, malaise and nausea occurred in a group of 19 out of 45 vaccinated soldiers (44 females, 1 male) participating as volunteers in this trial (Protocol HBV-003-89). The above symptoms appeared several hours following the first dose, lasted for about 12 hours and resolved spontaneously, with no long-term consequences. An extensive clinical and laboratory work-up excluded an organic etiology, resulting in a diagnosis of mass hysteria." The Applicant notes that a randomized comparative study was conducted following this episode and no vaccine-related safety events were identified. Additional information was provided in

125737/0.31. Of these 45 soldiers, all were vaccinated at the same site on the same day and additional doses were suspended in all 45 soldiers, who were subsequently withdrawn from the study, regardless whether symptoms were experienced. Subjects underwent physical and laboratory examinations, which did not reveal a specific diagnosis. Both batches of vaccine used in the trial were subjected to safety testing on mice and guinea pigs at the Ministry of Health Standards and Control Institute and by the manufacturer. The manufacturer also assessed the level of pyrogens and sterility. Sterility tests were also performed on the syringes and needles. All test results were reported to be negative and/or within normal limits. The same batches were confirmed to be used in other studies without similar incident.

Reviewer comment: *The above symptoms appear to describe acute vaccine-related systemic reactions. The above events were reported by the Applicant as mild. It appears that appropriate investigations were undertaken at the time of the event. In the pivotal trials, with the current formulation of Sci-B-Vac, myalgia was the only solicited systemic symptom reported more frequently compared to Engerix-B. An identical syndrome leading to discontinuation from treatment was not seen in the pivotal trials or in the other supportive trials.*

With the exception of the acute systemic reactogenicity leading to treatment discontinuation in approximately half of subjects in HBV-003-89 in 1991, the immunogenicity and the safety results of the above supportive trials were consistent with the results from the pivotal trials.

10. CONCLUSIONS

The Applicant submitted two Phase 3, randomized, double-blind, active-controlled studies evaluating a three-dose series of Sci-B-Vac in 2,920 adults ≥18 YOA who had never been vaccinated against HBV and who received at least one dose of Sci-B-Vac. In both studies, non-inferiority to Engerix-B, a US-licensed HBV vaccine was demonstrated based on the SPR, the proportion of subjects achieving anti-HBs ≥10 mIU/mL. The seroresponse rate observed one month following the third dose of Sci-B-Vac in healthy adults 18-45 YOA enrolled in Sci-B-Vac-002 was 99.3% (95% CI: 98.7, 99.6), and in adults ≥18 YOA enrolled in Sci-B-Vac-001 was 91.4% (95% CI: 89.1, 93.3). Manufacturing equivalence of three consecutive lots was also demonstrated based on SPR. In Sci-B-Vac-001, although declines in SPR were noted associated with age and other clinical factors, for the subgroups evaluated, SPRs were generally similar to or greater than the active control.

In subjects ≥18 YOA, local and/or systemic reactogenicity, generally of short duration, were reported in the majority of subjects evaluated following Sci-B-Vac. In general, the occurrence of local and systemic reactogenicity was greater in younger age groups and was highest following the first dose. Severe reactogenicity was uncommon. Unsolicited AEs were generally reported in similar proportions of subjects in the Sci-B-Vac and Engerix-B groups. Overall, in both pivotal studies, SAEs were reported at a higher frequency following Sci-B-Vac group compared to following Engerix-B. Rates and types of individual SAEs were generally consistent with the characteristics of study population enrolled and there were no patterns identified indicative of a relationship to vaccination. Routine pharmacovigilance will surveil for rare AEs which may require a larger sample size to be observed.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 48. Risk-Benefit Considerations of Vaccination with Sci-B-Vac in Adults ≥18 Years of Age

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Clinical manifestations of acute HBV infection may range from subclinical hepatitis to fulminant hepatic failure. Chronic hepatitis B infection may cause a chronic carrier state or progress to hepatic cirrhosis, liver failure, liver cancer, and death. • Globally, nearly 300 million people are estimated to be chronically infected with HBV. • In the US, routine universal HBV vaccination of infants and children has led to a significant decline in the rate of acute HBV infection to 1.0 per 100,000 (2019). The age group with the highest incidence of acute hepatitis B in the US is 40-49 years. • The risk of developing chronic HBV infection decreases with increasing age at the time of infection and is higher in immunosuppressed persons, including individuals on hemodialysis, with HIV infection, and with diabetes. Approximately 5% of acute hepatitis B infections in adults progress to chronic infection. • ACIP recommends HBV vaccination for all adults 19 – 59 YOA and those ≥60 YOA with risk factors for HBV infection. Adults ≥60 YOA without risk factors may also be vaccinated.	• Chronic hepatitis B can cause cirrhosis, liver cancer, and death, and remains a worldwide public health challenge. • Acute hepatitis B infection declined sharply in the US in association with universal childhood vaccination. However, many adults in the US are unvaccinated and at risk of acquiring HBV. • Immunocompromised adults, including those with diabetes, are at greater risk of developing chronic HBV infection than immunocompetent adults.
Unmet Medical Need	• Four licensed vaccines are available for the prevention of HBV in adults and adolescents in the US, Engerix-B (GSK), Recombivax HB (Merck), Heplisav-B (Dynavax), and Twinrix (GSK), a combination vaccine which includes a hepatitis A component. • These vaccines have been shown to be highly effective in controlled clinical trials evaluating the antibody response against hepatitis B surface antigen. • Long-term studies indicate that immune memory to hepatitis B post-vaccination remains intact for up to three decades post-immunization, even though anti-HBs antibody concentrations may become low or undetectable over time. • Medical and behavioral characteristics, including smoking, obesity, aging, chronic medical conditions, drug use, diabetes, male sex, and immune suppression, have been associated with a decreased response to some HBV vaccines.	• HBV vaccines are potentially lifesaving and widely used. • Several effective hepatitis B vaccines are currently licensed in the US that offer long-term protection against hepatitis B in immunocompetent adults. • Additional safe and effective vaccines against hepatitis B would allow greater flexibility for healthcare providers and patients.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• Two Phase 3, randomized, double-blind, active-controlled, pivotal clinical trials were submitted. • In Sci-B-Vac-002, in healthy adults 18-45 YOA, an SPR of 99.3% (95% CI: 98.7, 99.6) was observed 4 weeks after the third dose. • In Sci-B-Vac-001, in adults ≥18 YOA, an SPR of 91.4% (95% CI: 89.1, 93.3) was observed 4 weeks after the third dose. The study population included adults with chronic medical conditions. • In both trials, non-inferiority to the licensed comparator was demonstrated. • SPR decreased with increasing age group in Sci-B-Vac-001 (18-44 YOA: 99.2%, 45-64 YOA: 94.8%, ≥65 YOA: 83.6%), but to a lesser degree than in the same age groups in the Engerix-B arm (18-44 YOA: 91.1%, 45-64 YOA: 80.1%, ≥65 YOA: 64.7%). • While enrollment into some subgroups was too low to be able to draw conclusions, overall, the analyses suggest that immunogenicity results were generally consistent across age groups, genders, diabetic status, body mass index (BMI), and smoking status.	• Clinical benefit, as determined by SPR, was demonstrated to be non-inferior to a licensed comparator HBV vaccine. • An effective immune response was observed following Sci-B-Vac in the demographic and clinical subgroups evaluated.
Risk	• Local and systemic adverse reactions were commonly reported. In Sci-B-Vac-001, 71.9% and 55.9% of adults ≥18 YOA reported solicited local and systemic symptoms following Sci-B-Vac administration, respectively. In Sci-B-Vac-002, 85.0% and 68.2% of adults 18-45 YOA reported solicited local and systemic symptoms following Sci-B-Vac administration, respectively. Most reactogenicity events were mild or moderate and of short duration. • Severe reactogenicity was uncommon with <3.5% of subjects in either study reporting severe local or systemic reactogenicity. • Most solicited symptoms were reported more frequently after the first dose compared to doses 2 and 3. • Solicited local and general symptoms were reported more frequently in subjects 18-44 YOA compared to ≥45 YOA subjects. • A small increase in the proportion of subjects reporting SAEs in the 1 year following the first dose of Sci-B-Vac compared to following Engerix-B for both studies. SAEs were typical for the study populations and no specific safety signal was identified.	• Mild to moderate reactogenicity was reported more frequently following Sci-B-Vac than following Engerix-B. Severe reactogenicity was similar in both treatment groups. • Risk of vaccination with Sci-B-Vac appears to be minor relative to the demonstrated benefit.
Risk Management	• The proposed pharmacovigilance plan includes routine pharmacovigilance activities. • An observational pregnancy registry is planned as a postmarketing commitment.	• As proposed, the pharmacovigilance plan is adequate to manage the risk of Sci-B-Vac vaccination.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA establishes a substantial likelihood of benefit of vaccination with Sci-B-Vac in individuals ≥18 YOA based upon an established immune correlate of protection against HBV. Reactogenicity of short duration was commonly reported after Sci-B-Vac administration and was reported at higher proportions in younger compared to older individuals. Severe reactogenicity was uncommon. While there was a slightly greater proportion of subjects reporting SAEs in the Sci-B-Vac group compared to the active control, there was no evidence of vaccine-relatedness. The risk-benefit profile of Sci-B-Vac supports approval in individuals ≥18 YOA.

11.3 Discussion of Regulatory Options

The Applicant requested and the data support traditional approval of Sci-B-Vac in individuals 18 YOA and older.

11.4 Recommendations on Regulatory Actions

The clinical reviewer recommends approval of Sci-B-Vac for the prevention infection of all known subtypes of hepatitis B virus in individuals 18 YOA and older.

11.5 Labeling Review and Recommendations

The proprietary name, Prehevbrio, was reviewed and agreed upon by the primary review team in consultation with the Office of Compliance and Biologics Quality and Advertising and Promotional Labeling Branch.

CBER requested several changes to the proposed prescribing information, including the following revisions: presentation of the solicited AEs to separate by pivotal trial and age group, and to include solicited AE rates following each dose number and solicited AE duration; focus of the unsolicited AEs and SAEs on events assessed as related to vaccination (reactions); focus of the efficacy information on pertinent primary or secondary endpoints; and edits to multiple sections to align with pertinent regulations as well as information and language generally used in prescribing information for CBER products. Labeling negotiations were ongoing at the time the clinical review was finalized.

11.6 Recommendations on Postmarketing Actions

CBER requested the Applicant's commitment to conduct a pregnancy registry.

Reviewer's comment: *CBER concurred with the Applicant's proposed timeline and synopsis for the pregnancy registry postmarketing commitment. Please refer to Section 4.6 and the PV review for further details regarding postmarketing activities and pharmacovigilance.*