Summary Basis for Regulatory Action

Date:	November 30, 2021
From:	Marian Major, Supervisory Microbiologist, Review Committee Chair, OVRR/DVP
BLA/NDA STN:	STN 125737
Applicant:	VBI Vaccines (Delaware), Inc.
Submission Receipt Date:	November 30, 2020
Action Due Date:	November 30, 2021
Proper Name:	Hepatitis B Vaccine (Recombinant)
Proprietary Name:	PREHEVBRIO
Indication:	Prevention of infection caused by all known subtypes of the hepatitis B virus in adults 18 years of age and older

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

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Director, Office of Compliance and Biologics Quality

Discipline Reviews - Office/Division	Reviewer/Consultant
CMC • CMC Product (OVRR/DVP) • Facilities review (OCBQ/DMPQ) • Facilities SBRA (OCBQ/DMPQ) • Remote Interactive Evaluation Report (OCBQ/DMPQ and OVRR/DVP) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	 Lauren Siltz, PhD Priscilla M. Pastrana, PhD Debra Vause Priscilla M. Pastrana, PhD Lauren Siltz, PhD Marian Major, PhD Varsha Garnepudi, MS Noel Baichoo, PhD Hyesuk Kong, PhD Tao Pan, PhD
Clinical • Clinical (OVRR/DVRPA) • Postmarketing safety epidemiological review (OBE/DE) • BIMO (OCBQ/DIS)	 Darcie Everett, MD, MPH Margarita Gomez-Lorenzo, MD Bhanu Kannan, MS
Statistical • Clinical data (OBE/DB) • Non-clinical data (OBE/DB)	 Jennifer Kirk, PhD Jennifer Kirk, PhD
Non-clinical/Pharmacology/Toxicology • Toxicology (OVRR/DVRPA) • Developmental toxicology (OVRR/DVRPA) • Animal pharmacology (OVRR/DVP)	 Ching-Long Sun, PhD Ching-Long Sun, PhD Marian Major, PhD
Labeling • Promotional (OCBQ/APLB) • Carton/Container (OVRR/DVRPA) • Package Insert (OVRR/DVRPA)	 Twanda Scales Oluchi Elekwachi, PharmD, MPH Daphne Stewart Paul Keller, PhD
Other Review(s) not captured above categories, for example: • Regulatory Project Manager (OVRR/DVRPA)	 Paul Keller, PhD Katherine Berkhousen
Advisory Committee Summary	Not Applicable

Table of Contents

1. Introduction

On November 30, 2020, VBI Vaccines Inc. (the Applicant) submitted a biologics license application (BLA) for licensure of a recombinant hepatitis B vaccine. The proper name of the vaccine is Hepatitis B Vaccine (Recombinant). The Applicant originally proposed 3-antigen, Hepatitis B Vaccine (Recombinant) as the proper name. It was considered by the review team that this could be interpreted to imply a tri-valent vaccine, which would be misleading as this vaccine does not provide protection against more viral variants than any of the currently licensed hepatitis B vaccines. The proposed proprietary name is PREHEVBRIO. The vaccine is also referred to as Sci-B-Vac in communications from the Applicant and in some sections of this SBRA. The proposed indication is for active immunization to prevent infection caused by all known subtypes of the hepatitis B virus in adults 18 years and older. PREHEVBRIO is a recombinant hepatitis B vaccine produced

in Chinese hamster ovary (CHO) cells that have been genetically modified to produce the hepatitis B virus (HBV) envelope proteins: the small (S), middle (pre-S2), and large (pre-S1) hepatitis B surface antigens (HBsAg). Currently U.S.-licensed yeast-derived hepatitis B vaccines contain the small S protein alone. CHO cells (b) (4) HBsAg. The (b) (4) aluminum hydroxide adjuvant, and filled into single-dose vials. The drug substance (DS) and drug product (DP) are manufactured at SciVac Ltd., Rehovot, Israel, a subsidiary of VBI Vaccines Inc. Labeling and packaging operations also occur at SciVac Ltd.

PREHEVBRIO (1 mL dose) is a sterile suspension for intramuscular (IM) injection, containing 10 mcg HBsAg adsorbed to aluminum hydroxide [$Al(OH)_3$] (0.5 mg aluminum) (b) (4) . The immunization regimen consists of three doses administered at 0, 1, and 6 months. The vaccine does not contain preservative. The proposed shelf-life of the final container product is 36 months at 5±3°C from the date of manufacture, which is defined as the date of initiation of filling of the DP into final containers.

2. Background

HBV infects the liver and can cause both acute and chronic disease. Worldwide more than 2 billion people have been infected with HBV, with approximately 250 million persons chronically infected (1). Acute HBV infection progresses to chronic infection in approximately 5% of healthy adults (2); progression is greater among those with co-morbidities, such as those with diabetes and immunocompromised persons (3).

The World Health Organization estimated that hepatitis B resulted in ~800,000 deaths in 2019, mostly from cirrhosis and hepatocellular carcinoma (4). Following the recommendation for universal childhood vaccination in the U.S. in 1991 (5), the incidence of acute HBV infection decreased from approximately 8.5 per 100,000 (1990) to 1.0 per 100,000 (2019) (6). The CDC estimated that there were up to 20,700 acute HBV infections in 2019, with ~80% occurring in adults aged 30-59 years (6). Of the 13,859 new chronic hepatitis B cases reported to the CDC in 2019, 47% occurred in persons aged 30-49 years (6). In the U.S. prevalence is currently ~850,000 (7), and HBV infection causes ~1,600 deaths annually (6).

Transmission of HBV is by percutaneous and mucosal exposure to infectious blood or body fluids. Nosocomial transmission between patients and from patients to health care workers, including those working in hemodialysis and oncology units, has become rare, declining 95% since implementation of routine vaccination and standard precautions for blood-borne pathogens (3). Chronic hepatitis B infection can be treated with antiviral therapy. However, in most cases treatment suppresses viral replication but does not cure infection. Therefore, treatment must be continued for life.

Three licensed vaccines against hepatitis B are currently available for adults in the U.S. All are made from yeast-derived recombinant S antigen. ENGERIX-B (GSK) and RECOMBIVAX HB (Merck) are adsorbed onto aluminum compounds. HEPLISAV-B (Dynavax Technologies, Corp.) is combined with a novel cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant (CpG 1018 adjuvant). There is also one combination vaccine for adults, TWINRIX (GSK), which includes a hepatitis A vaccine component. ENGERIX-B, RECOMBIVAX HB and TWINRIX are approved for use in adults as a three-dose series

to be administered at months 0, 1 to 2, and 6 to 12. An accelerated schedule is licensed for TWINRIX as a series of four doses (1 mL each), given on days 0, 7, and 21 to 30, followed by a booster dose at month 12. HEPLISAV-B is approved for use in adults aged 18 and above as a two-dose series to be administered at months 0 and 1.

The currently licensed vaccines contain only the small S antigen from HBV. PREHEVBRIO contains the medium (pre-S2) and large (pre-S1) in addition to the small S antigen. The Applicant hypothesizes that the inclusion of the three forms of HBsAg results in the secretion from CHO cells of particles that are morphologically, biochemically and antigenically similar to naturally occurring HBV particles and that this leads to a conformationally appropriate presentation of epitopes to the immune system and potentially improved immunogenicity.

PREHEVBRIO was initially licensed in Israel in 2000 under the name Sci-B-Vac and has since been approved and marketed in countries in Asia, Africa, and South America for indications against HBV infection in healthy children and adults as a 3-dose regimen delivered at months 0, 1 and 6. Sci-B-Vac has been licensed at 3 dose levels: 2.5 mcg HBsAg/0.5 mL and 5 mcg HBsAg/0.5 mL for use in neonates, infants, and children; and 10 mcg HBsAg/1 mL for adolescents and adults. Sci-B-Vac is currently marketed in Israel and Hong Kong.

Prevention of disease is no longer required to establish effectiveness of HBV vaccines. Effectiveness of PREHEVBRIO was assessed by determining the seroprotection rate (SPR): the proportion of subjects with an anti-hepatitis B surface antigen (anti-HBs) level ≥10 mIU/mL, an antibody concentration recognized as conferring protection against HBV infection (8, 9). To support licensure in the U.S., two Phase 3 clinical studies (Sci-B-Vac-001 and Sci-B-Vac-002) comparing PREHEVBRIO to ENGERIX-B were conducted in North America and Europe using the three-dose regimen. Sci-B-Vac-001 was a comparative study against ENGERIX-B, designed to demonstrate non-inferiority in adults ≥18 years old, based on the SPR 4 weeks after the third dose and to evaluate the safety of PREHEVBRIO compared to ENGERIX-B. Sci-B-Vac-002 was a lot-to-lot consistency study, designed to establish the manufacturing consistency of PREHEVBRIO, based on the 2-sided 95% confidence interval (CI) of the ratio of the geometric mean concentration (GMC) of anti-HBs for all pairwise comparisons between three lots of PREHEVBRIO. As a secondary objective, the immunogenicity and safety of PREHEVBRIO were compared to ENGERIX-B.

Table 1. PREHEVBRIO Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	April 10, 2017
2. IND submission (IND 17542)	July 26, 2017
3. Type-C meeting (CRMTS#11948)	October 3, 2019
4. Pre-BLA meeting (IND 17542)	May 13, 2020
5. BLA 125737/0 submission	November 30, 2020
6. BLA filed	January 29, 2021
7. Mid-cycle communication	May 25, 2021
8. Late-cycle meeting	September 2, 2021
9. Action Due Date	November 30, 2021

3. Chemistry Manufacturing and Controls (CMC)

No significant CMC issues were identified during review of the BLA. Several Information Requests for additional documentation or clarification were sent to the Applicant. Responses to all requests were received and found to be satisfactory.

a. Product Quality

The information provided in the BLA for the HBV vaccine PREHEVBRIO demonstrates that the manufacturing process is well controlled with appropriate validations and in-process control testing. Moreover, adequate quality control testing has been conducted and stability data have been accrued with the DS and DP.

Drug Substance

PREHEVBRIO is a recombinant vaccine produced by expression of three related pre-S1, pre-S2, and S protein components of HBsAg in CHO cells. (b) (4)

(b) (4)

Both the DS and DP are manufactured at SciVac Ltd. in Rehovot, Israel (FEI: 3012695367). This facility is not currently licensed for manufacture of any U.S.-licensed vaccines. The facility is dedicated to the production of HBsAg for PREHEVBRIO.

Manufacture

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

Drug Product

PREHEVBRIO DP is a sterile, aqueous suspension delivered in single-dose vials intended for intramuscular injection. Each dose (1.0 mL) is formulated to contain 10 mcg/mL of HBsAg adsorbed on aluminum hydroxide [$Al(OH)_3$)] as an adjuvant (aluminum content of 0.5 mg/mL), 8450 mcg sodium chloride, 20 mcg potassium chloride, 380 mcg disodium hydrogen phosphate dodecahydrate, and 20 mcg potassium di-hydrogen phosphate anhydrous. From the manufacturing process, each 1.0 mL dose may also contain trace amounts of formaldehyde, CHO cell protein, CHO cell DNA, and BSA.

PREHEVBRIO is supplied as a single-dose in 4 mL glass vials fitted with a rubber injection stopper, sealed with an aluminum seal with a plastic, colored flip-off top. The vial stoppers are not made with natural rubber latex. The vaccine does not contain preservative.

Manufacture

Manufacture of PREHEVBRIO is performed at the SciVac Ltd. facility in Rehovot, Israel. The process begins with the DS and consists of (b) (4), formulation, aseptic filling, and packing. The duration of the DP manufacturing process is approximately (b) (4) there are no hold steps during DP formulation.

(b) (4)

DP is filled into 4 mL (b) (4) mL nominal capacity) ready-to-fill (RTF) (b) (4) glass vials at a concentration of 10 mcg/mL, with a fill volume of (b) (4) mL to allow withdrawal of the labeled 1.0 mL volume. Filling is performed at (b) (4). The filled, stamped, and labeled vials are stored at 2-8°C. Visual inspection of 100% of the vials in each batch is performed by qualified personnel at (b) (4). After visual inspection, vials are sampled from (b) (4) of filling, and lot release tests are performed.

Labeling is performed at the SciVac Ltd. facility dedicated to the labeling and packaging of the DP. Labeling is performed at (b) (4) and vials (b) (4). Labeled vials are returned to 2-8°C storage until secondary packaging is performed. Secondary packaging boxes consist of 10 vials per unit.

The control strategy includes process controls, in-process tests, process validation and release specifications, as well as analytical methods.

Control of Materials

Raw Materials: There are no materials of human or animal origin used in the DP manufacturing process.

Impurities: Potential DP-specific impurities are (b) (4) and leachables from the DP container closure system. (b) (4) is monitored as part of the release and stability testing. An assessment of the potential impurities (b) (4) in aluminum hydroxide was performed by the supplier and no risks were identified.

Specifications and Methods: The proposed tests, specifications, and methods for the release of the PREHEVBRIO DP are shown in Table 4. Stability analytical methods and acceptance criteria are the same as those used for DP release except for the container volume, which is not performed for stability.

Table 4. PREHEVBRIO DP Release and Stability Tests and Specifications

Test	Method	Acceptance Criteria
Physical inspection	Visual inspection	Turbid when mixed, clear colorless upper solution and white precipitate upon settling
Identity	HBsAg S protein (b) (4)	(b) (4)
(b) (4)		
Aluminum content	(b) (4)	
Volume in container	Container content for injections, (b) (4)	1 mL vial (b) (4) (Not performed for stability)
In vivo potency	By (b) (4)	(b) (4)
(b) (4)		
Endotoxin	(b) (4)	
Sterility	(b) (4)	No growth
Container closure integrity (CCI)	(b) (4)	

Extractables and Leachables: No risks identified.

Stability of the Drug Product and Proposed Shelf-life: The proposed shelf life for PREHEVBRIO DP is 36 months at 5±3°C and is supported by (b) (4) primary stability DP lots that were placed on stability for (b) (4) months. (b) (4) will be placed on stability

each year at 5±3°C for (b) (4) months, with vials (b) (4) to represent the worst-case scenario. Testing will be performed at months 3, 6, 12, 24 and (b) (4)

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the PREHEVBRIO DS and DP were found to be adequate for their intended use.

c. Center for Biologics Evaluation and Research (CBER) Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture and testing of PREHEVBRIO [Hepatitis B Vaccine (Recombinant)] are listed in Table 5. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 5: Manufacturing Facilities for PREHEVBRIO [Hepatitis B Vaccine (Recombinant)]

Name/Address	FEI number	DUNS number	Inspection/Remote Interactive Evaluation/Waiver	Results/ Justification
SciVac Ltd. 13 Gad Feinstein Rd POB 580, Rehovot 7610303, Israel Drug Substance (DS) and Drug Product (DP) manufacturing, DP release testing, DP labeling and packaging	3012695367	514477301	Remote Interactive Evaluation (RIE)	CBER October 18-21 and October 25-26, 2021 Acceptable
(b) (4)			Waiver	ORA (b) (4) VAI
(b) (4)	(b) (4)		Waiver	CDER (b) (4) VAI

Name/Address	FEI number	DUNS number	Inspection/Remote Interactive Evaluation/Waiver	Results/ Justification
(b) (4)			Waiver	ORA (b) (4) NAI
(b) (4)			Waiver	ORA (b) (4) NAI

CDER= Center for Drug Evaluation and Research
ORA= Office of Regulatory Affairs
VAI= Voluntary Action Indicated
NAI = No Action Indicated

CBER used its authority under section 704(a)(4) to request records in advance or in lieu of an inspection and also conducted a RIE of SciVac Ltd. in Rehovot, Israel from October 18-21 and October 25-26, 2021 for the DS and DP manufacturing and the testing of PREHEVBRIO. The 704(a)(4) records request and the RIE were conducted due to travel restrictions. At the conclusion of the RIE, a RIE observation memo was issued with two observations. The firm's response to these observations was received on November 16, 2021 and the corrective actions were reviewed and found to be adequate. All RIE issues have been satisfactorily resolved.

(b)(3)

The Office of Regulatory Affairs (ORA) conducted a surveillance inspection of the (b) (4) from (b) (4). The inspection was classified Voluntary Action Indicated (VAI). All inspectional issues were resolved.

The Center for Drug Evaluation and Research (CDER) conducted a surveillance inspection of (b) (4) from (b) (4). The inspection was classified VAI. All inspectional issues were resolved.

ORA conducted a surveillance inspection of (b) (4) . from (b) (4) The inspection was classified No Action Indicated (NAI). No issues were identified.

ORA conducted a surveillance inspection of (b) (4) from (b) (4) The inspection was classified NAI. No issues were identified.

e. Container/Closure System

The DP is filled into a 4 mL (b) (4) clear borosilicate glass vial with a 7 mm opening (b) (4) stoppered with a 7.5 mm black chlorobutyl (b) (4) rubber injection stopper (b) (4) and sealed with a 15 mm (b) (4) aluminum seal with a light blue plastic flip-off top cap (b) (4) The container closure integrity testing was conducted by SciVac Ltd. employing the (b) (4) method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Toxicology: Three toxicity studies and an intramuscular embryo-fetal developmental and pre- and post-natal reproductive toxicity study in rats were submitted.

All three toxicity studies were not GLP compliant. In the first two toxicity studies, the dosing regimen did not mimic the proposed trial and the test article was not the intended clinical formulation, therefore no conclusions could be drawn. For the third study, an 8-week repeated dose toxicity study, the testing facility was not GLP certified at the time the study was performed in 2004. The report did not contain line listings of the individual data points, including laboratory data points. Based on the limited data submitted, the vaccine caused typical location reactions at the injection sites but did not cause any systemic effects other than the expected lymphoid hyperplasia.

In the embryo-fetal developmental toxicity study, three groups of female rats were administered intramuscularly placebo control, placebo adjuvant control or 10 mcg HBsAg and (b) (4) mcg $Al(OH)_3$ 30 days and 15 days prior to mating, and on gestation days 4 and 15. Half of the pregnant rats were sacrificed on gestation day 21 for embryo-fetal development assessment and the other half were delivered for pre- and post-natal development assessment. There were no female reproductive effects and no effects on fetal/embryonal development and postnatal development up to day 23.

Non-clinical Pharmacology: The Sci-B-Vac product has been marketed in countries outside the U.S. for several years and immunogenicity data from previous clinical studies were provided by the Applicant to demonstrate vaccine effectiveness. Data from one non-clinical pharmacological study (Study 26BC02A) were submitted to demonstrate the benefit of $Al(OH)_3$ adjuvant addition to the 10 mcg/mL HBsAg Sci-B-Vac for the induction of humoral immune responses in (b) (4) mice and to compare the potency of Sci-B-Vac adjuvanted vaccine to ENGERIX-B. Mice were immunized with Sci-B-Vac either with or without $Al(OH)_3$ adjuvant or with ENGERIX-B. The data demonstrated that the inclusion of $Al(OH)_3$ adjuvant with Sci-B-Vac improved antibody responses.

Overall, the nonclinical toxicity assessments provided in the submission did not raise significant safety concerns. Despite the deficiencies in the general toxicology studies, prior clinical experience with the vaccine outside the U.S. for several years was sufficient to support further development under the U.S. IND.

5. Clinical Pharmacology

No clinical pharmacology or pharmacokinetic studies were performed in the clinical development program for PREHEVBRIO. No studies were performed on special populations.

6. Clinical/Statistical

a. Clinical Program

Overview of Clinical Trials

In support of approval for use of PREHEVBRIO in individuals ≥18 years of age (YOA), the Applicant submitted the results of Sci-B-Vac-001 and Sci-B-Vac-002, two randomized, observer-blind, active-controlled trials in adults, including 2,920 subjects who received at least one dose of PREHEVBRIO. Effectiveness of a three-dose series on days 1, 28, and 168 (0, 1 and 6 months) was evaluated based on non-inferior immunogenicity to a U.S.-licensed comparator 4 weeks after the third dose as measured by the SPR, the proportion of subjects achieving serum anti-HBs ≥10 mIU/mL, an established correlate of protection for HBV infection. In each of the trials, collection of safety data was similar and included solicited local (injection site pain, tenderness, pruritis, redness, and swelling) and systemic (nausea/vomiting, diarrhea, headache, fatigue, myalgia, and fever) adverse reactions recorded on a diary card by all subjects for 7 days following each vaccination, unsolicited adverse events (AEs) recorded on a diary card for 28 days following each vaccination, and serious AEs (SAEs), medically attended AEs (MAAEs), and new-onset chronic illnesses (NOCIs) from the first vaccination through 6 months following the third vaccination. Both studies assessed hematology and chemistry laboratory parameters following each vaccination in a subset of at least 10% of subjects.

Sci-B-Vac-001 was a Phase 3, multi-center, multi-national, observer-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 1 dose of a three-dose series of PREHEVBRIO or ENGERIX-B (active control) administered on days 1, 28, and 168. Two co-primary objectives were defined by the Applicant: 1) demonstration of non-inferior immunogenicity of PREHEVBRIO 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 statistically superior immunogenicity of PREHEVBRIO to ENGERIX-B at day 196 in adults ≥45 YOA. The first co-primary endpoint was CBER's primary basis for licensure. Subjects were followed for safety and immunogenicity from first vaccination through day 336, approximately 6 months following the third dose of vaccine.

Sci-B-Vac-002 was a Phase 3, multi-center, multi-national, observer-blind, randomized, active-controlled trial to evaluate the manufacturing consistency, immunogenicity and safety of PREHEVBRIO. A total of 2,836 HBV vaccine-naïve adults 18-45 YOA were enrolled and received at least 1 dose of a three-dose series of one of three independent lots of PREHEVBRIO or with ENGERIX-B (active control) administered on days 1, 28, and 168. The primary objective was evaluation of manufacturing equivalence between

the three PREHEVBRIO lots as determined by geometric mean concentration (GMC) ratios of anti-HBs at day 196, 4 weeks after the third dose. The secondary objective was demonstration of non-inferior immunogenicity of PREHEVBRIO 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.

Demographic and Baseline Characteristics

Subjects 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 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%).

Clinical Effectiveness

Effectiveness of PREHEVBRIO was assessed by determining the SPR: the proportion of subjects with an anti-HBs level ≥10 mIU/mL, an antibody concentration recognized as conferring protection against HBV infection.

The clinical reviewer and the statistical reviewer agreed that vaccine effectiveness was demonstrated in Sci-B-Vac-001 and Sci-B-Vac-002. The data submitted to the BLA demonstrated that in all clinical studies, the primary immunogenicity endpoint of seroprotection with PREHEVBRIO met the non-inferiority criterion when compared with ENGERIX-B.

Sci-B-Vac-001: 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 vaccinations, had evaluable serum immunogenicity samples at baseline and day 196, and had no protocol deviations leading to exclusion (PREHEVBRIO group N=718, ENGERIX-B group N=723). The SPR was 91.4% (95% CI: 89.1, 93.3) in the PREHEVBRIO group and 76.5% (95% CI: 73.2, 79.5) in the ENGERIX-B group. 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-inferior immunogenicity of PREHEVBRIO compared to ENGERIX-B 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 (PREHEVBRIO group N=625, ENGERIX-B group N=627). In the FAS, SPR at Day 196 was 89.4% (95% CI: 86.8, 91.7) in the PREHEVBRIO group and 73.1% (95% CI: 69.4, 76.5) in the ENGERIX-B group, resulting in a difference in SPR (PREHEVBRIO −ENGERIX-B) of 16.4% (95% CI: 12.2, 20.7), meeting the prespecified criterion (lower bound of the 95% CI of the difference in SPR was > 0%).

Sci-B-Vac-002: 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 vaccinations, had evaluable serum immunogenicity samples at baseline and day 196, and had no protocol deviations leading to exclusion (PREHEVBRIO Lot A N=620, PREHEVBRIO Lot B N=622, PREHEVBRIO Lot C N=627). In the PPS1, mean, adjusted GMCs of anti-HBs at day 196 were 5,882.3 mIU/mL, 4,821.7 mIU/mL, and 5,569.9 mIU/mL across Lots A, B, and C of PREHEVBRIO, 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 boundaries of [0.67, 1.5], and therefore lot-to-lot consistency was demonstrated.

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 PREHEVBRIO group N=1,753, ENGERIX-B group N=592). In the PPS2, the SPR was 99.3% (95% CI: 98.7, 99.6) in the pooled PREHEVBRIO group and 94.8% (95% CI: 92.7, 96.4) in the ENGERIX-B group. 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-inferior immunogenicity of PREHEVBRIO compared with ENGERIX-B 4 weeks after the third vaccination was demonstrated in subjects 18-45 YOA.

Clinical Serology Assay: Measurement and Analysis of the Immune Response to PREHEVBRIO

The Applicant used a commercial assay, the VITROS ECi/ECiQ Immunodiagnostic Systems, to assess antibodies to hepatitis B surface antigen (anti-HBs). This is an automated system. The testing was performed by a contract lab, (b) (4) (b) (4) . The VITROS anti-HBs quantitative assay is performed using the VITROS Anti-HBs Quantitative Reagent Pack and VITROS Immunodiagnostic Products Anti-HBs Calibrators on the VITROS ECi/ECiQ VITROS 5600 Integrated System using Intellicheck Technology. The assay has been approved by the Center for Devices and Radiological Health (CDRH) for quantifying anti-HBs antibodies.

Validation data for the use of the VITROS anti-HBs quantitative assay at (b) (4) to assess seroconversion and anti-HBs titers was submitted to the BLA and to IND 17542/9 and found to be appropriately validated for the intended use.

The method involves the reaction of anti-HBs in the sample with hepatitis B S antigen (ad and ay subtypes) coated onto wells. A horseradish peroxidase (HRP)-labeled hepatitis B S antigen conjugate (ad and ay subtypes) then complexes with the bound anti-HBs forming an “antigen sandwich.” The bound HRP conjugate is measured by a luminescent reaction. A reagent containing luminogenic substrates is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The light signals are read by the VITROS ECi/ECiQ Immunodiagnostic System. The amount of HRP conjugate bound is directly proportional to the concentration of anti-HBs present in the sample.

The limit of detection for the assay was reported by the manufacturer as 4.23 mIU/mL. A value of <5 mIU/mL is recorded as negative, a value of >5 mIU/mL and <12 mIU/mL is recorded as intermediate and a value ≥12 mIU/mL is recoded as positive.

b. Bioresearch Monitoring (BIMO)

BIMO inspections were conducted at three domestic clinical investigator sites participating in the conduct of study protocols Sci-B-Vac-001 and Sci-B-Vac-002 and one domestic clinical investigator site participating in the conduct of study protocol Sci-B-Vac-002. The inspections did not reveal substantive problems impacting the data submitted in support of this BLA.

c. Pediatrics

The FDA Pediatric Review Committee (PeRC) convened on October 12, 2021, to consider the proposal for a full waiver of pediatric studies in the PREHEVBRIO developmental program.

The majority of PeRC members agreed to a full pediatric waiver for all pediatric subgroups. The waiver is being granted due to no meaningful therapeutic benefit over existing therapies and the product is not likely to be used in a substantial number of pediatric patients. Some of the discussion points included:

- There are 4 vaccines currently licensed for vaccination against hepatitis B in children. Two are single component vaccines (ENGERIX-B and RECOMBIVAX-HB) approved for use in all pediatric age groups and two are combination vaccines (PEDIARIX and VAXELIS) approved for use in subsets of the pediatric population (6 weeks through 6 years and 6 weeks through 4 years, respectively). These combination vaccines are preferred over monovalent hepatitis B vaccines in the relevant pediatric age groups per the Advisory Committee on Immunization Practices (ACIP). The current hepatitis B vaccines are very effective in the pediatric population with seroprotection rates of 96%-100%.
- With approval of PREHEVBRIO in adults, the Prescribing Information (PI) will clearly state the age range (i.e., 18 years of age and older) for which use is approved and there is no expectation that the ACIP would recommend this vaccine for use in the pediatric population.

d. Other Special Populations

Pregnancy was an exclusion criterion for Sci-B-Vac-001 and Sci-B-Vac-002. No clinical data are available to address the use of PREHEVBRIO during lactation. PREHEVBRIO was not evaluated in immunocompromised subjects and adults on hemodialysis in the pivotal or supportive trials. Among subjects 65 through 86 years of age who received PREHEVBRIO, the SPR was 83.6% of those ≥ 65 years of age compared to 94.8% in adults 45 through 64 years of age and 99.2% in adults 18 through 44 years of age.

7. Safety and Pharmacovigilance

Reactogenicity, particularly local, occurred in a majority of subjects. Severe reactogenicity was uncommon and reactions typically resolved in 1-2 days. There were no notable patterns or numerical imbalances between vaccination groups for specific categories of serious adverse events that would suggest a causal relationship to PREHEVBRIO. The data demonstrate substantial evidence of effectiveness, as well as safety, and are supportive of licensure of PREHEVBRIO 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 postmarketing.

Sci-B-Vac-001 Safety Summary

Safety was evaluated in the Safety Set, consisting of subjects who received at least one dose of study product (PREHEVBRIO N=796, ENGERIX-B N=811). Injection site (IS) pain and tenderness were the most commonly reported solicited local adverse reactions after PREHEVBRIO 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 PREHEVBRIO and ENGERIX-B groups, respectively. Myalgia, headache, and fatigue were the most commonly reported solicited systemic adverse reactions after PREHEVBRIO 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 PREHEVBRIO and ENGERIX-B groups, respectively. Myalgia was the only solicited systemic adverse reaction reported at a clinically significantly higher frequency in the PREHEVBRIO group compared to the ENGERIX-B group. Fever was uncommon, reported by 0.8% and 1.1% of subjects in the PREHEVBRIO and ENGERIX-B groups, respectively. In both groups, the percentage of subjects reporting solicited reactogenicity was generally highest following the first dose and was lower following subsequent doses.

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% PREHEVBRIO and 21 subjects, 2.6% ENGERIX-B). One SAE of viral gastroenteritis occurring 5 days after dose two of PREHEVBRIO was assessed by the investigator as related and by the Applicant and CBER as not related to vaccination. No clinically significant differences were noted with respect to the nature or timing of the 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 Safety Summary

In the Safety Set for Sci-B-Vac-002 (pooled PREHEVBRIO group N=2124, ENGERIX-B group N=712) IS pain and tenderness were the most commonly reported solicited local adverse reactions after PREHEVBRIO 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 PREHEVBRIO and ENGERIX-B groups, respectively. Myalgia, fatigue, and headache were the most commonly reported solicited systemic adverse reactions after PREHEVBRIO 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 PREHEVBRIO and ENGERIX-B groups, respectively. Myalgia was the only solicited systemic adverse reaction reported at a clinically significantly higher frequency in the PREHEVBRIO group than in the ENGERIX-B group. Fever was uncommon, reported by 1.1% of subjects in both groups. In the PREHEVBRIO group, local and systemic solicited adverse reactions tended to be reported at the highest frequencies following the first dose, with the exception of IS pruritis 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 PREHEVBRIO.

In the Safety Set, SAEs were reported more frequently in the PREHEVBRIO group (42 subjects, 2.0%) than in the ENGERIX-B group (3 subjects, 0.4%). A 35-year-old man died of sudden cardiac death due to hypertrophic heart disease (b) (6) days after dose 1 of

PREHEVBRIO. This death was assessed by the investigator as unrelated and CBER agrees with this assessment. Otherwise, SAEs consisted of conditions generally typical of the age and health of the study population, with infections and injuries being the most commonly reported classes of events. No SAEs were assessed as related, and the nature or timing of the SAEs did not suggest a vaccine-related safety concern. 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. No vaccine-related clinically significant safety laboratory abnormalities were identified.

Safety Conclusions

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 PREHEVBRIO 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 PREHEVBRIO group compared to the ENGERIX-B group (74 subjects, 2.5% PREHEVBRIO and 24 subjects, 1.6% ENGERIX-B), while SAEs within 28 days of any vaccination were reported at relatively similar rates between groups (25, subjects, 0.9% PREHEVBRIO and 9 subjects, 0.6% ENGERIX-B). Four subjects in the PREHEVBRIO 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 vaccination groups.

8. Labeling

The proposed proprietary name, PREHEVBRIO, was reviewed by the Advertising and Promotional Labeling Branch (APLB) May 7, 2021 and found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on June 18, 2021.

APLB reviewed the proposed PI, package, and container labeling on September 27, 2021 and made several comments and recommendations from a promotional and comprehension perspective. These were accepted by the Applicant and all changes were found to be acceptable. Division of Vaccines and Related Products Applications (DVRPA) reviewed the proposed carton and container labels and made several comments and recommendations. These were communicated to and accepted by the Applicant.

The review team conveyed to the applicant multiple recommended and requested revisions to the PI. All labeling issues regarding the PI and the carton and container labels were resolved following communications with the Applicant.

9. Advisory Committee Meeting

This submission was not discussed at a Vaccines and Related Biological Products Advisory Committee meeting because FDA review of information submitted in the BLA, including the clinical study design and trial results, did not raise any concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

There were no other regulatory issues.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the review of the clinical, nonclinical, and product-related data submitted in this original BLA submission, the Review Committee recommends approval of PREHEVBRIO for the labeled indication and usage.

b. Benefit/Risk Assessment

Considering the data submitted to support the safety and effectiveness of PREHEVBRIO that have been presented and discussed in this document, the Review Committee is in agreement that the risk/benefit analysis of PREHEVBRIO is favorable and supports approval for the use PREHEVBRIO in adults 18 years and older for the prevention of infection caused by all known subtypes of the hepatitis B virus.

c. Recommendation for Postmarketing Activities

The Office of Biostatistics and Epidemiology (OBE) concluded that the Pharmacovigilance Plan (PVP) adequately reflects safety concerns based on clinical trial experience and postmarketing data provided. OBE agreed with routine pharmacovigilance, as proposed by the Applicant in the PVP, with adverse event reporting as required under 21 CFR 600.80. The reviewed data do not indicate a need for a postmarketing requirement study or a Risk Evaluation and Mitigation Strategy safety program. OBE recommended that a Pregnancy Registry be a postmarketing commitment (PMC) and the Applicant agreed to establish a pregnancy registry on November 9, 2021. The PMC wording is as follows:

To establish a pregnancy registry to prospectively collect data on reported exposures to PREHEVBRIO during pregnancy and evaluate pregnancy and fetal/neonatal outcomes. The registry will collect information from 120 pregnant women.

Final protocol submission: February 1, 2022

Study/clinical trial completion: March 1, 2032

Final report submission: December 1, 2032

12. References

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