



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
(CBER) Division of Epidemiology (DE)**

**PHARMACOVIGILANCE ORIGINAL BLA
MEMORANDUM**

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To: Marion Major, PhD
Chair of the Review Committee

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Subject: Review of Pharmacovigilance Plan

Sponsor: VBI Vaccines Inc.

Product: PREHEVBRIO, Hepatitis B vaccine (recombinant, 3-antigen)

**Application Type
/Number:** BLA/ STN 125737/0

Proposed Indication: Active immunization for prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

Submission Date: November 30, 2020

Action Due Date: November 30, 2021

This product was also referred to as *Sci-B-Vac* in the clinical development.

1 Objective

The purpose of this review is to assess the adequacy of the pharmacovigilance plan (PVP) based on the safety profile of PREHEVBRIO.

2 Product Information

2.1 Product description

PREHEVBRIO [Hepatitis B vaccine (recombinant), 3 antigen] is manufactured by recombinant DNA technology in Chinese Hamster Ovary mammalian cells and contains the full antigenic structure of the HBV surface antigen, including the small (S), middle (pre-S2) and large (pre-S1) hepatitis B surface antigens. PREHEVBRIO is formulated with aluminum hydroxide as an adjuvant, along with excipients consisting of sodium chloride (NaCl), potassium chloride (KCl), disodium hydrogen phosphate dodecahydrate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$), potassium dihydrogen phosphate anhydrous (KH_2PO_4) and water for injections.

PREHEVBRIO is a sterile aqueous suspension manufactured in single-dose vials for intramuscular injection. A single dose vial contains 10 µg of non-infectious, recombinant Hepatitis B surface antigens (pre-S1, pre-S2 and S) in the 1.0 mL dose.

2.2 Proposed dosing regimen(s) and formulation(s)

The product is administered as a series of three doses (1.0 mL each) by intramuscular injection at months 0, 1 and 6 in adults 18 years of age and older.

3 Materials Reviewed

Table 1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
	VCI Vaccines Inc.	BLA Sequence 001	Modules: 1.14.1.3 Draft Labeling Text 1.16 Core Risk management Plan 2.7.4 Summary of clinical safety 5.3.5.3 Integrated summary of safety
	VCI Vaccines Inc.	BLA Sequence 007	Module: 1.11.3 Clinical Information Amendment <ul style="list-style-type: none"> • Response to FDA's April 16, 2021 Information Request
	VCI Vaccines Inc.	BLA Sequence 0011	Module: 1.16.1 Risk management (Non-REMS) <ul style="list-style-type: none"> • PREHEVBRIO Pregnancy Outcomes Registry Synopsis (DRAFT / June 2, 2021) • Pregnancy Report Form, version 1.0, and version 2.0
	VCI Vaccines Inc.	BLA Sequence 0020	Module 1.11.3 Clinical Information Amendment <ul style="list-style-type: none"> • Response to FDA's July 2, 2021 Information Request • SMQ of anaphylactic reaction • SMQ of Hypersensitivity reaction • Summary of Pregnancies in Sci-B-Vac Supportive Studies
	VCI Vaccines Inc.	BLA Sequence 0021	Module 1.11.3 Clinical Information Amendment <ul style="list-style-type: none"> • Response to FDA's August 16, 2021 Information Request

	VCI Vaccines Inc.	BLA Sequence 0025	Module 1.11.3 Clinical Information Amendment <ul style="list-style-type: none"> Response to FDA's August 31, 2021 Information request
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4 Summary of Prior Marketed Experience

The product was originally approved in Israel in 2000 (under the tradename Bio-Hep-B) and the current formulation is registered in Israel and Hong Kong. The product has also been previously registered in 15 other countries in South America, Africa, and Asia (under the trade name Sci-B-Vac or Bio-Hep-B).

PREHEVBRIO 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 (09 February 2000) to data lock point (14 June 2020), the estimated number of vials of Sci-V-Bac sold is (b) (4). Assuming that all subjects completed the recommended 3-dose regimen, the cumulative exposure to the product has been estimated to be approximately (b) (4) subjects.

An IR was sent to the sponsor on April 16, 2021 (STN # 125737/0/6) requesting a 5-year analysis of post-marketing data for the time period April 2016 to April 2021. In the Sponsor's response, they provided data describing a total of 3 post-marketing reports involving 3 adult individuals who experienced 8 non serious adverse events (AEs) after being vaccinated with PREHEVBRIO. The reports are described below:

- A 22-year-old female experienced non-related foot and palm pain, primarily during movement one week after vaccination which resolved after 3.5 weeks.
- A 49-year-old male experienced throat pain, pharyngitis, lymphadenopathy (neck), fever and glossopharyngeal neuralgia one day after vaccination, which resolved after 18 days.
- A 69-year-old with a past medical history of renal insufficiency (hemodialysis), heart disease, diabetes and metabolic syndrome who experienced serum ALT (144 IU/L) elevation and HBs antigenemia two days after vaccination with the 20 µg dose, which resolved after 20 days.

Reviewer comment:

In the response to FDA's August 31, 2021 IR, the sponsor attributes the low number of post-marketing safety reports to the favorable safety profile of the vaccine (mainly administered to healthy adults) and a limited distribution of the vaccine in the market (about (b) (4) subjects received all 3 doses from 2016 to 2021). The report of transient HBs antigenemia is reported in the literature in patients administered standard hepatitis B vaccine dosages (1-2) and with increased dosages used for hemodialysis patients (3). HBsAg positivity is clinically insignificant and is described in the Draft Labeling of PREHEVBRIO, Section 7.2. Interference with Laboratory Tests.

5 Description of Product Safety Database

5.1 Clinical studies

Of the 13 clinical trials in adults included in this application, the primary data that support the safety and tolerability of PREHEVBRIO are the pooled safety data from the 2 pivotal Phase 3 trials: Sci-B-Vac-001 and Sci-B-Vac-002. The pivotal studies were randomized double-blind, placebo-controlled trials comparing the safety of PREHEVBRIO with the control vaccine, Engerix-B. Data from the other 11 supportive trials in adults were not pooled due to variances in formulations, dose levels of antigen, and/or methods of safety data collection.

Sci-B-Vac-001 was a double-blind randomized controlled trial designed to establish the non-inferiority of PREHEVBRIO compared to Engerix-B in adults ≥ 18 years of age and the superiority of PREHEVBRIO compared to Engerix-B in adults ≥ 45 years old. Study subjects were randomized 1:1 to receive either a total of 3 intramuscular (IM) injections of PREHEVBRIO or 3 IM injections of Engerix-B (one injection on Study Day 1 one injection at 4 weeks [Study Day 28] and one injection at 24 weeks [Study Day 168]) and were followed for 24 weeks after receiving the third vaccination until Study Day 336).

Sci-B-Vac-002 was a double-blind randomized controlled trial conducted to assess the lot-to-lot consistency of PREHEVBRIO and to compare the immunogenicity and safety of a three-dose

regimen of PREHEVBRIO to a three-dose regimen of Engerix-B in adults 18-45 years old. Study subjects were randomized 1:1:1:1 to receive either a total of 3 IM injections of PREHEVBRIO lot A, 3 IM injections of PREHEVBRIO lot B, 3 IM injections of PREHEVBRIO lot C or 3 IM injections of Engerix-B (one injection on Study Day 0, one injection at 4 weeks [Study Day 28] and one injection at 24 weeks [Study Day 168]) and were followed for 24 weeks after receiving the third vaccination until Study Day 336).

Safety follow-up telephone calls were conducted 7 days after each vaccination to inquire about \geq Grade 3 local and systemic reactions. Safety evaluations included standardized methods for local and systemic vaccine reactions using a diary card, vital signs, and physical examinations, and a 48-week follow-up for SAEs, medically attended events, or new onset of chronic illness events, and changes in concomitant medication.

In addition, a clinical laboratory sub-study, including at least 10% of the total number of subjects enrolled to the trial, assessed hematology and biochemistry laboratory parameters (1 week after each vaccination) over the full 3-dose vaccination schedule.

The pooled safety data from these 2 pivotal Phase 3 trials includes a total of 4,443 unique subjects, 2,920 of whom received PREHEVBRIO.

5.2 Adverse events

Solicited Adverse Events:

Local:

Rates of solicited local AEs within 7 days of any vaccination reported in the PREHEVBRIO and Engerix-B groups were 81.4% and 55.7%, respectively. This difference was largely attributable to higher frequencies of injection site pain (72.2% and 44.5%) and tenderness (71.2% and 44.2%) in the PREHEVBRIO group compared to the Engerix-B group.

The severity of solicited local AEs after any vaccination in subjects receiving PREHEVBRIO and Engerix-B respectively was Grade 1: 50.2% vs 44.2%, Grade 2: 28.3% vs 10.0%, Grade 3: 2.4% vs 0.9%, and Grade 4: 0.5% vs 0.7%.

Grade 3 solicited local AEs developed in 71 subjects in the PREHEVBRIO group (2.4%) and 13 (0.9%) subjects in the Engerix-B group.

A total of 25 Grade 4 solicited local AEs occurred in 24 subjects [14 (0.5%) in PREHEVBRIO, 10 (0.7%) in Engerix-B groups], including 20 AEs of erythema and 5 AEs of swelling at the injection site. These events were programmatically

classified by default as Grade 4 based on subject-reported exfoliative dermatitis/skin necrosis at the injection site that was entered on the diary card (in one case the report was entered in error by the clinical site). These AEs were not medically-attended and could not be confirmed. Based on the measurement of the greatest diameter of redness or swelling (between 0 and 50 mm), the highest severity of these AEs would be classified as Grade 1. Therefore, there was no concordance in severity between the reports of exfoliative dermatitis/skin necrosis (Grade 4) and the actual local skin reaction (Grade 1 erythema and swelling). During safety follow-up calls, there were no reports of local or systemic AEs of Grade 3 or higher severity. All of these events resolved within 1-7 days of vaccination.

There were 8 individuals in the PREHEVBRI0 group compared with 6 in the Engerix-B group who recorded exfoliative dermatitis/skin necrosis at the injection site on the diary card after receiving the 1st or 2nd dose of the vaccine. All recipients completed their 3-dose regimen, and none reported a subsequent episode of exfoliative dermatitis/skin necrosis on their diary cards.

Systemic:

Solicited systemic AEs were reported at a higher rate in the PREHEVBRI0 group compared to the Engerix-B group (64.7% vs. 54.1%) primarily due to a higher rate of myalgia in the PREHEVBRI0 group (41.7% vs 28.1%).

The severity of systemic AEs after any vaccination in subjects receiving PREHEVBRI0 and Engerix-B respectively was Grade 1: 40.7% vs 32.6%, Grade 2: 21.1% vs 18.9%, Grade 3: 2.8% vs 2.6% and Grade 4: 0.1% vs 0%.

Grade 3 solicited systemic AEs developed in 81 subjects in the PREHEVBRI0 group (2.8%) and 40 in the Engerix-B group (2.6%).

Grade 4 solicited systemic AEs occurred in 3 subjects in the PREHEVBRI0 group:

- One subject developed fatigue (Day 5 to Day 7) after the second vaccination of PREHEVBRI0 and did not require medical attention.
- One subject developed headache (Day 4 to Day 7) after the third vaccination of PREHEVBRI0.
- One subject developed nausea and vomiting, which occurred on Day 5 after the third vaccination of PREHEVBRI0. This AE was part of an SAE of vertigo, which occurred at the same time and which was assessed as unrelated to study vaccine. The SAE resolved within 5 days, the subject recovered with no sequelae and completed the study as planned.

Grade 4 solicited systemic AEs did not occur in subjects in the Engerix-B group.

Reviewer comment:

Solicited local events were more frequent among recipients of PREHEVBRIO, however, most solicited local AEs were of Grade 1 to Grade 2 severity. Grade 3 and 4 AEs were uncommon in both groups. Reports of exfoliative dermatitis/skin necrosis entered by subjects on diary cards were not medically treated or confirmed. All subjects in both groups who reported exfoliative dermatitis/skin necrosis successfully completed the 3-dose vaccination series.

Solicited systemic events were also more frequent among recipients of PREHEVBRIO, however Grade 3 and Grade 4 systemic solicited AEs were uncommon and balanced between both groups. Of note, these events of higher severity did not preclude participants from completing vaccination series and did not reappeared with subsequent doses of the vaccine.

Treatment Emergent Adverse Events

The rates of Treatment-Emergent Adverse Events (TEAEs) 28 days after any vaccination in PREHEVBRIO and Engerix-B groups were 52.9% and 53.3%, respectively. Most of the TEAEs that occurred within 28 days of vaccinations were of Grade 1 or Grade 2 in severity. Grade 3 and Grade 4 TEAEs within 28 days of any vaccination were reported by 6.3% and 6.4%, of subjects in the PREHEVBRIO and Engerix-B groups, respectively. The most frequently reported AEs that occurred within 28 days of any vaccination were: headache (11.0% vs. 10.0%), upper respiratory tract infection (8.4% vs. 7.6%), nasopharyngitis (4.6% vs. 4.8%), fatigue (3.9% vs. 3.7%), dysmenorrhea (3.2% vs. 2.4%), back pain (3.1% vs. 2.6%), myalgia (2.9% vs. 3.4%), oropharyngeal pain (2.7% vs. 2.6%), and injection site pain (2.4% vs. 1.6%).

The rate of related TEAEs 28 days after any vaccination in PREHEVBRIO and Engerix-B groups were 13.0% and 15.2%, respectively. Grade 3 and Grade 4 events assessed by the investigator as vaccine-related that occurred in >1 subject in either vaccine group included gastroenteritis (2 PREHEVBRIO subjects).

Reviewer comment:

The overall rates of Treatment-Emergent Adverse Events (TEAEs) and related TEAEs 28 days after any vaccination were balanced between in PREHEVBRIO and Engerix-B. Most TEAEs were assessed as Grade 1 or Grade 2 in severity and unrelated to vaccination. There were no clusters or unusual patterns of TEAEs.

Rates of Grade 3 and Grade 4 TEAEs within 28 days of any vaccination were low and reported at similar rates by the PREHEVBRIO and Engerix-B groups. Related TEAEs of Grade 3 or 4 severity were infrequent among PREHEVBRIO recipients and were limited to 2 cases of gastroenteritis.

Deaths:

Only one death was reported in the clinical trial: This death was a report of sudden cardiac death secondary to hypertrophic heart disease (SUDDEN CARDIAC DEATH) that occurred in a 35-year-old black male randomized to PREHEVBRIO (Sci-B-Vac-002 study). The subject received the first dose of study vaccine on (b) (6) (Day 1). (b) (6) (Day ^{(b) (6)} days after receiving the first dose of the study vaccine, the subject died due to sudden cardiac death secondary to hypertrophic heart disease. Post-mortem examination revealed evidence of past open-heart surgery and biventricular hypertrophy. Autopsy and toxicological examination confirmed the cause of death to be sudden cardiac death due to hypertrophic heart disease. The Investigator assessed causality as unrelated to the study vaccine.

Reviewer comment:

Death was reported in one participant in the 2 pivotal Phase 3 trials (1/2,920). The reviewer agrees with the assessment of causality of sudden cardiac death as unrelated to PREHEVBRIO given the subject's ongoing medical history and autopsy findings.

SAEs:

SAEs were reported by 74 (2.5%) subjects in the PREHEVBRIO group and 24 subjects (1.6%) in the Engerix-B group. The SAEs reported in >2 subjects who received PREHEVBRIO were appendicitis (4 subjects) and intervertebral disc protrusion (3 subjects). No SAEs reported in >2 subjects who received Engerix-B.

One SAE (0.1%) of viral gastroenteritis was assessed by the investigator as related to PREHEVBRIO; the event occurred within 28 days of vaccination. The sponsor assessed the event as unrelated to study vaccine.

The following unrelated SAEs developed in the PREHEVBRIO group only:

- A White US male in 75-84 years-old elderly sub-group developed Grade 1 peroneal nerve palsy within 28 days of administration of Dose #1.

Note: There was one case of Grade 2 peroneal nerve palsy that occurred within 28 days of Dose#2 in a subject in the Engerix-B group that was reported as a non-serious event.

- A White European male in the 18-44 years-old age group developed vestibular neuronitis 122 days after administration of Dose # 3.

- A White US female in the 65-74 years age group developed Grade 3 rheumatoid arthritis within 28 days of Dose #3. The subject was diabetic and had a BMI >30.

Reviewer comment:

Serious adverse events were uncommon in both treatment arms and SAEs occurring in > 2 subjects were uncommon. The reviewer agrees with the assessment of causality provided by the sponsor for the SAE of viral gastroenteritis as unrelated to vaccination.

Subjects with solicited adverse events leading to vaccine withdrawal and or discontinuation of study:

- In the PREHEVBRIO group:
 - A 19-year-old female experienced a related Grade 1 related headache after Dose #1, leading to both vaccine withdrawal and discontinuation of study.
 - A 41-year-old male experienced a related Grade 2 related fatigue after Dose #2, leading to vaccine withdrawal.
 - A 45-year-old female experienced a related Grade 3 fatigue after Dose #2, leading to vaccine withdrawal.
- In the Engerix-B group:
 - A 71-year-old female experienced a Grade 3 related myalgia after Dose #2 leading to both vaccine withdrawal and discontinuation of study.
 - A 37-year-old female experienced pruritus (not graded), fatigue (Grade 1) and headache (Grade 2) after Dose #2, leading to both vaccine withdrawal and discontinuation of study.

Reviewer comment:

Solicited adverse events leading to vaccine withdrawal and or discontinuation of study were uncommon and balanced among both vaccine groups.

6 Sponsor's Pharmacovigilance Plan

The sponsor's Core Risk management Plan lists Missing Information as a safety concern only. There were no important Identified or Potential Risks.

Table 9. Summary table of the Pharmacovigilance Activities and Risk Minimization Activities by safety concern. Core Risk management Plan – version 13 Nov 2020 (page 42, BLA sequence 001).

Safety concern	Risk minimization	Pharmacovigilance activities
#1. Use in patients simultaneously being administered other vaccines	Routine risk minimization measures: <i>Included in the USPI label, section 7.1: when concomitant administration of PREHEVBRIO and immune globulin is required, they should be given with different syringes at different injection sites; if concomitant administration of other vaccines is required, these should be given with a different syringe at different injection sites.</i>	Routine pharmacovigilance activities

Safety concern	Risk minimization	Pharmacovigilance activities
<p>#2. Seroconversion in patients with immunological function impairment</p>	<p>Routine risk minimization measures: <i>Included in USPI section 5.2: immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to PREHEVBRIO.</i></p>	<p>Routine pharmacovigilance activities</p>
<p>#3. Use in pregnancy</p>	<p>Routine risk minimization measures: <i>Included in USPI section 8.1: PREHEVBRIO should be used during pregnancy when there is a clear risk of hepatitis B infection and when benefit outweighs the risks.</i> <i>Included in USPI section 8.1: women who receive PREHEVBRIO during pregnancy are encouraged to contact a dedicated number set up for calls by VBI Inc.</i></p>	<p>Routine pharmacovigilance activities</p> <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Pregnancy Exposure Registry that monitors pregnancy outcomes in women exposed to PREHEVBRIO within 28 days following the LMP (last menstrual period) or at any time during pregnancy. The estimated enrolment is 40-50 participants over 7 years with a planned start date on March 1, 2022 and completion date on December 31, 2028. Follow-up activities are initiated in pregnancy cases (e.g., due date for follow-up is the estimated delivery date + 2 weeks). Spontaneous reports of exposure during pregnancy will be followed up using Pregnancy Form (Appendix 1). The final protocol will be submitted on February 1, 2022. The final study report will be submitted on March 1, 2029.

Safety	Risk minimization	Pharmacovigilance activities
#4. Use during breast-feeding	Routine risk minimization measures: <i>Included in USPI section 8.2: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PREHEVBRIO and any potential adverse effects on the breastfed child from PREHEVBRIO or from the underlying maternal condition.</i>	Routine pharmacovigilance activities

7 Analysis of Sponsor's Pharmacovigilance Plan

7.1 Important Potential or Identified Risks: None

7.2 Missing information: Use in patients simultaneously being administered other vaccines.

The 2 pivotal phase 3 clinical trials (Sci-V-Bac-001 and Sci-V-Bac-002) excluded subjects immunized with attenuated vaccines (e.g., Measles, Mumps, Rubella) within 4 weeks prior to enrolment and subjects immunized with inactivated vaccines (e.g., influenza) within 2 weeks prior to enrolment. The reason for exclusion was to avoid a confounded interpretation of efficacy study endpoints and safety evaluation.

Reviewer comment:

Routine risk minimization measures will address this in the PI:

-Section 7.1, when concomitant administration of PREHEVBRIO and immune globulin is required, they should be given with different syringes at different injection sites.

-Section 7.1, if concomitant administration of other vaccines is required, these should be given with different syringes at a separate injection site.

With some exceptions, simultaneously administering the most widely used live and inactivated vaccines has produced seroconversion rates and rates of adverse events similar to those observed when the vaccines are administered separately (4-7). It is acceptable to add this item as missing information. DE will review relevant post-marketing data for this through routine pharmacovigilance.

7.3 Missing information: Seroconversion in patients with immunological function impairment

The seroconversion rate in patients with immunological function impairment (autoimmune diseases, primary immunodeficiency, secondary immunodeficiency) is not known as those subjects were excluded from participation in the 2 pivotal Phase 3 trials (Sci-V-Bac-001 and Sci-V-Bac-002). Seroconversion rates in other groups of subjects excluded from the pivotal trials due to the criteria below are unknown and meet the criteria of missing information but are not included as such in the PVP:

-Any history of cancer requiring chemotherapy or radiation within 5 years of randomization or current disease.

-Treatment by immunosuppressant within 30 days of enrolment including but not limited to corticosteroids at a dose that is higher than an oral or injected physiological dose, or >20 mg/day prednisolone equivalent.

Reviewer comment:

Routine risk minimization measures will address this in the PI:

-Section 5.2, immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to PREHEVBRIO.

It is acceptable to add these items as missing information. DE will review relevant post-marketing data on vaccine failure in patients with immunological function impairment, history of cancer requiring chemotherapy or radiation within 5 years of vaccination or current disease and treatment by immunosuppressant within 30 days of vaccination through routine pharmacovigilance.

7.4 Missing information: Use in pregnancy

Studies on reproductive toxicity and embryo/fetal development study were conducted in (b) (4) rats receiving PREHEVBRIO at a 10 µg IM dose, in a volume of 0.5 mL, split between 2 sites. PREHEVBRIO and controls (placebo and placebo/adjuvant) were administered to F0 females on Day 30 and Day 15 before mating and on Gestation Day (GD) 4 and Gestation Day 15 (total of 4 doses). Groups 2 and 5 received PREHEVBRIO, Groups 1 and 4 animals (control) received placebo, while Groups 3 and 6 animals received placebo+Al(OH)₃ adjuvant.

The pregnancy rate was 100% in the PREHEVBRIO group, 96% in the controls, and 92% in the placebo group. There were no adverse effects on reproduction, including pregnancy rate, gestation index, live birth index and litter size. The gestation index was 100% in the PREHEVBRIO group, control, and placebo+Al(OH)₃ adjuvant groups. There were no animals with total resorption and no adverse effects on live or dead pups, or pre-and post-implantation losses.

The Sponsor identified exposure during pregnancy to PREHEVBRIO as missing information, since pregnant women were excluded from the 2 pivotal Phase 3 trials (Sci-V-Bac-001 and Sci-V-Bac-002).

Pregnancy was reported for 18 subjects who received PREHEVBRIO and 2 subjects who received Engerix-B. A total of 4 subjects in the PREHEVBRIO group (3 of 4 subjects received 2 vaccinations with PREHEVBRIO; 1 subject received only 1 vaccination with PREHEVBRIO) reported an AE associated with pregnancy which included:

- Vomiting in pregnancy (outcome of pregnancy was a healthy male infant)
- Subchorionic hemorrhage and fetal demise due to large subchorionic hemorrhage. Noninvasive pre-natal test for trisomy 21 was positive and subsequently confirmed by chorionic villus biopsy.
- Abortion spontaneous
- Ankyloglossia congenital

No other adverse events were associated with pregnancy.

The pregnancy outcome for the 18 subjects who received PREHEVBRIO was as

follows:

- Healthy/no anomalies at birth: 9
- Fetal demise (associated with large subchorionic hemorrhage with trisomy 21 confirmed by chorionic villus biopsy; pregnancy was high risk – elderly multigravida): 1
- Miscarriage (PT: abortion spontaneous): 1
- Ankyloglossia congenita: 1
- Elective termination: 4
- Unknown: 2

The pregnancy outcome for the 2 subjects who received Engerix-B was as follows:

- Elective termination: 1
- Unknown: 1

Reviewer comment:

Given the paucity of data in pregnant women who received PREHEVBRIO, use in pregnancy is acceptable to be listed as missing information. Routine risk minimization measures will address this in the PI:

-Section 8.1, PREHEVBRIO should be used during pregnancy when there is a clear risk of hepatitis B infection and when benefit outweighs the risks.

The sponsor proposes to monitor this missing information with a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PREHEVBRIO during pregnancy and includes in the PI a dedicated number set up by the sponsor to enroll patients in the Pregnancy Registry. The sponsor plans to follow-up spontaneous reports of exposure during pregnancy by use of a pregnancy questionnaire form. Should this product be approved, DE recommends that the Pregnancy Registry will be a postmarketing commitment (PMC).

7.5 Missing information: Use during breast-feeding

The Sponsor identified exposure during breastfeeding to PREHEVBRIO as missing information, since breastfeeding women were excluded from the 2 pivotal Phase 3.

Reviewer comment:

In the absence of data in humans, it is not known whether the vaccine is excreted in human milk.

Routine risk minimization measures will address this in the PI:

- Section 8.2, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PREHEVBRIO and any potential adverse effects on the breastfed child from PREHEVBRIO or from the underlying maternal condition.

It is acceptable to add this item as missing information. DE will review this data through routine pharmacovigilance.

8.. DE Assessment

The sponsor's PVP adequately reflects safety concerns based clinical trial experience and postmarketing data provided.

9. DE Recommendations

DE agrees with routine pharmacovigilance, as proposed by the sponsor in the PVP, with adverse event reporting as required under 21 CFR 600.80. The reviewed data do not indicate a need for a post-marketing requirement study or a Risk Evaluation and Mitigation Strategy (REMS) safety program. Should this product be approved, DE recommends that the Sponsor's Pregnancy Registry will be a postmarketing commitment (PMC). Please see the final version of the package insert submitted by the sponsor for the final agreed-upon label language.

Summary of PVP

	Important Safety Concern	Pharmacovigilance Action
	Important identified safety concerns	
1	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • NA
	Important potential safety concerns	
2	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • N/A
	Important missing information	
3	<ul style="list-style-type: none"> • Use in patients simultaneously being administered other vaccines 	<ul style="list-style-type: none"> • Agree with sponsor-proposed action
	<ul style="list-style-type: none"> • Seroconversion in patients with immunological function 	<ul style="list-style-type: none"> • Agree with sponsor-proposed action
	<ul style="list-style-type: none"> • Use in pregnancy 	<ul style="list-style-type: none"> • Agree with sponsor-proposed action
	<ul style="list-style-type: none"> • Use during breast-feeding 	<ul style="list-style-type: none"> • Agree with sponsor-proposed action

References:

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- 4.- King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. *Pediatr Infect Dis J*. 1994;13(5):394-407.
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- 6.- Dashefsky B, Wald E, Guerra N, Byers C. Safety, tolerability, and immunogenicity of concurrent administration of *Haemophilus influenzae* type b conjugate vaccine (meningococcal protein conjugate) with either measles-mumps-rubella vaccine or diphtheria-tetanus-pertussis and oral poliovirus vaccines in 14- to 23-month-old infants. *Pediatrics*. 1990;85(4 Pt 2):682-689.
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