24 February 2022
EMA/CHMP/86102/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

PreHevbri

International non-proprietary name: hepatitis B surface antigen

Procedure No. EMEA/H/C/005466/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

$Al(OH)_3$	Aluminum Hydroxide
$AlPO_4$	Aluminum Phosphate
AE	Adverse Event
ACIP	Advisory Committee on Immunization Practices
ANCOVA	Analysis of Covariance
Anti-HBs	Hepatitis B Surface Antibody
BTG	Biotechnology General Ltd
BLA	Biologics Licensing Application
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HDV	Hepatitis D Virus
HIV	Human Immunodeficiency Virus
IBD	Inflammatory Bowel Disease
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (formerly the International Conference on Harmonisation)
IM	Intramuscular
IIS	Investigator Initiated Study
IND	Investigational New Drug
i.p.	intraperitoneal
ITT	Intent to Treat
LHBs	Large pre-S1 Surface Antigen
MHBs	Middle pre-S2 Surface Antigen
MAA	Marketing Authorization Application

MAAE	Medically Attended Adverse Event
NIHE	National Institute of Hygiene and Epidemiology
NOCI	New Onset of Chronic Illness
PBRER	Periodic Benefit Risk Evaluation Report
PPS	Per Protocol Set
PPS1	Per Protocol Set 1
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SHBs	S Hepatitis B Surface Antigen
SPR	Seroprotection Rate
TEAE	Treatment Emergent Adverse Event
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant VBI Vaccines B.V. submitted on 20 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for PreHevbri, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

PreHevbri is indicated for the prevention of infection caused by all known subtypes of the hepatitis B virus in adults.

It can be expected that hepatitis D will also be prevented by immunisation with PreHevbri as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0342/2019 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 January 2017	EMEA/H/SA/3454/1/2016/SME/III	*Prof. Dieter Deforce, Dr Filip Josephson*

31 January 2019	EMEA/H/SA/3454/1/FU/1/2018/SME/III	*Dr Walter Janssens, Dr Filip Josephson*

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Risk mitigation strategy regarding adventitious agent contamination; assessment of extractables, leachables and impurities; specifications for drug substance and product.
- Adequacy of the non-clinical package to support Phase III and MAA
- Adequacy of the planned clinical programme.
- Subgroup analyses, statistical considerations, safety assessment and blinding.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Ingrid Wang

The application was received by the EMA on	20 November 2020
The procedure started on	24 December 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 February 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to PreHevbri on	24 February 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

HBV infection causes a broad spectrum of disease severity from subclinical self-limiting infections to fulminant hepatitis or chronic infection. Up to 50% of adults develop symptomatic icteric hepatitis, which is characterized by fatigue, fever, anorexia, and jaundice. Acute HBV infection can develop into a chronic disease. The likelihood that HBV infection becomes chronic is age-dependent. While infants infected with HBV in the first year of life almost universally develop chronic infection, immunocompetent adults develop chronic hepatitis at a rate of 5-10%. Immunosuppressed individuals, including those with diabetes and older adults are at an increased risk of developing chronic HBV. In adults, while acute HBV symptoms are typically transient and self-limiting, among those who become chronically infected with HBV, 20-30% will develop cirrhosis or liver cancer.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Transmission

HBV is highly transmissible, and is 50-100 more infectious than the human immunodeficiency Virus. Main modes of transmission are by exposure of mucosal membranes or dermal lesions to infected blood or body fluids (saliva, sperm, vaginal fluids). HBV infection can occur during birth, from an infected mother to her baby and or by sharing toothbrushes, razors, percutaneous instruments (needles, syringes) or having sexual contact with an infected individual.

Epidemiology

Recent estimates of the number of people chronically infected with HBV have ranged from 240 million to 350 million globally, with more than two billion humans ever having been infected. In the United States (US), though it is estimated that approximately 850,000 people are chronically infected with HBV, the actual number may be as high as 2.2 million, due to incomplete disease surveillance for viral hepatitis. It is estimated that 4.7 million people living in the European Union (EU) and the European Economic Area (EEA) countries are chronically infected with the HBV. Of the cases reported in Europe in 2017 (at a rate of 7.2 per 100 000 population), 15,472 (58%) were chronic. Notification rates varied by country, ranging from <0.1 per 100,000 population in Romania to 18.0 per 100,000 population in Iceland, with the United Kingdom (UK) reporting 62% of all chronic cases. The geographical variation likely reflects differences in local testing and reporting practices as well as underlying epidemiological differences.

Globally, liver cancer is one of the most common causes of cancer-related deaths. Over half of which are the result of chronic HBV. Incidence rates for liver cancer among Americans have increased 38% from 2003 to 2012, and liver-cancer related deaths have increased 56% from 2003 to 2012. In Europe, 28% of liver cancer cases have been attributed to chronic HBV infection. It is estimated that one fifth of the cases of HBV associated cirrhosis and liver cancer is caused by HDV. The higher rates of comorbid conditions in older individuals are likely to increase the risk of complications from both acute HBV infection and chronic liver disease, thus altering the clinical manifestation of HBV disease in this population.

Hepatitis B screening

Most international guidelines recommend that several high-risk groups be screened for HBsAg, and that those at risk and not immune should be offered hepatitis B vaccination.

Guidelines recommend that persons at high risk for HBV infection should be screened. For example, the Centers for Disease Control and Prevention (CDC) updated 2008 guidelines recommend testing injection drug users, men having sex with men, persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastro-enterologic disorders. The recommendation also includes persons with elevated ALT/AST of unknown aetiology, donors of blood, plasma, organs, tissues, or semen, all pregnant women, infants of HBsAg-positive mothers. Moreover, household, needle-sharing, or sex contacts of persons known to be HBsAg positive, and HIV-positive persons should be screened.

HBV has three antigens (surface, core, and e), some of which can be detected in the blood. The body's immune response produces antibodies tailored to each type of antigen (surface antibody, core antibody, and e antibody), which can also be detected from a blood test. The basic blood test for hepatitis B consists of the following three screening tests. A hepatitis B surface antigen test determines whether a person currently has the infection. A hepatitis B core antibody test determines whether a person has ever been infected, and a hepatitis B surface antibody test determines whether a person has cleared the virus after infection, or has been vaccinated and is now immune to future infections.

Prevention and unmet need

Recombinant DNA-derived vaccines against HBV have been available for more than two decades. The primary hepatitis B immunization series conventionally consists of three doses of vaccine. Vaccination of infants and, in particular, delivery of hepatitis B vaccine within 24 hours of birth is 90–95% effective in preventing infection with HBV as well as decreasing HBV transmission if followed by at least two other doses. WHO recommends universal hepatitis B vaccination for all infants, and that the first dose should be given as soon as possible after birth.

In the EU, the recommendations for adult HBV vaccination reflect regional differences in the hepatitis B vaccination program, which depend on the epidemiology of HBV in the region and logistic considerations and are largely based on targeted risk-group vaccination strategies. Adults who were not immunized as children remain at risk of becoming infected with HBV. Up to 10% of all adults fail to achieve seroprotective levels of antibodies against HBV (i.e. anti-HBs ≥10 mIU/mL) with a three-dose schedule of conventional HBV vaccines, and are considered "non-responders" to hepatitis B vaccination.

In addition to age and genetic factors, other factors are known to be associated with reduced immunogenicity of HBV vaccines in adults, including obesity, diabetes, smoking, and concomitant disease.

2.1.3. Biologic features, aetiology and pathogenesis

Viral hepatitis is an inflammation of the liver resulting from infection with a hepatitis virus. The pathogenesis and clinical manifestations of hepatitis B are due to the interaction of the virus and the host immune system, which leads to liver injury and, potentially, cirrhosis and hepatocellular carcinoma.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Hepatitis B signs and symptoms of acute hepatitis B may include abdominal pain, fever, loss of appetite, nausea, vomiting, weakness and fatigue, and jaundice. The diagnostic includes serological testing, liver ultrasound, and liver biopsy. It is not possible, on clinical grounds, to differentiate hepatitis B from hepatitis caused by other viral agents, hence, laboratory confirmation of the diagnosis is essential. The basic blood test for hepatitis B can determine whether a person currently has the infection, has ever been infected, has cleared the virus after infection, or has been vaccinated and is now immune to future infections. Acute HBV infection is characterized by the presence of HBsAg and immunoglobulin M (IgM) antibody to the core antigen, HBcAg. During the initial phase of infection, patients are also seropositive for hepatitis B e antigen (HBeAg). HBeAg is usually a marker of high levels of replication of the virus. The presence of HBeAg indicates that the blood and body fluids of the infected individual are highly infectious. Chronic infection is characterized by the persistence of HBsAg for at least 6 months (with or without concurrent HBeAg). Persistence of HBsAg is the principal marker of risk for developing chronic liver disease and liver cancer (hepatocellular carcinoma) later in life.

HBV infection causes a broad spectrum of disease severity from subclinical self-limiting infections to fulminant hepatitis or chronic infection. Up to 50% of adults develop symptomatic icteric hepatitis. The likelihood that HBV infection becomes chronic is age-dependent. While infants infected with HBV in the first year of life almost universally develop chronic infection, immunocompetent adults develop chronic hepatitis at a rate of 5-10%. Immunosuppressed individuals, including those with diabetes and older adults are at an increased risk of developing chronic HBV. Among those who become chronically infected with HBV, 20-30% will develop cirrhosis or liver cancer.

2.1.5. Management

There is no specific treatment for acute hepatitis B. Therefore, care is aimed at maintaining comfort and adequate nutritional balance, including replacement of fluids lost from vomiting and diarrhoea. Most important is the avoidance of unnecessary medications.

Chronic hepatitis B infection can be treated with antiviral agents. Treatment can slow the progression of cirrhosis, reduce incidence of liver cancer and improve long term survival.

2.2. About the product

PreHevbri is a recombinant, alum-adjuvanted hepatitis B vaccine, produced by expression of the Pre-S1, Pre-S2 and S protein components of hepatitis B virus (HBV) surface antigen (HBsAg) in Chinese Hamster Ovary (CHO) cells. PreHevbri was developed with the aim to produce a more immunogenic HBV vaccine, that would be better able to elicit an adequate immune response against HBV in those individuals with poor or delayed responses to the current second-generation yeast-derived HBV vaccines. Antigens from current licensed Hepatitis B vaccines are expressed in yeast host cells, whereas the antigens of PreHevbri are expressed in CHO mammalian cells. In contrast to yeast cells, CHO mammalian cells secrete HBV particles that resembles the naturally occurring HBV particles in terms of protein composition, glycosylation pattern and harbour all antigenic epitopes and domains of the HBV envelope which are present in PreHevbri. These characteristics may contribute to more conformationally appropriate presentation of the immunogenic epitopes to the immune system.

For use in adults, PreHevbri is presented as a sterile suspension for intramuscular [IM] injection in 1.0 mL single-dose vials, with each vial containing 10 µg/mL HBsAg with aluminium hydroxide [Al(OH)3] 0.5 mg/mL as an adjuvant.

2.3. Quality aspects

2.3.1. Introduction

The finished product ("PreHevbri") is presented as 1 mL sterile suspension for intramuscular injection containing 10 µg of hepatitis B surface antigens (S [83%], pre-S1 [11%] and pre-S2 [6%])) as active substance, adsorbed on 500 µg of Al^{3+} as aluminum hydroxide, hydrated.

Other ingredients are: sodium chloride, potassium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for injections.

The product is available in single-dose glass vial, fitted with a rubber stopper and sealed with an aluminum seal with a plastic coloured flip-off top.

2.3.2. Active Substance

2.3.2.1. General information

PreHevbri is a recombinant hepatitis B vaccine produced in mammalian Chinese Hamster Ovary (CHO) cells genetically modified to produce the hepatitis B virus envelope proteins, which include the small (S), middle (pre-S2) and large (pre-S1) hepatitis B surface antigens (HBsAg), representing the active substance. The manufacturing process yields particles with protein composition and glycosylation patterns that resemble wild type virions.

The HBsAg theoretical amino acid sequences were provided. Total amino acid analysis, N-terminal sequencing and determination of the primary protein structure were conducted in order to obtain confirmation of the bulk HBsAg structure. The individual surface antigens consist of 226 (S), 281 (pre-S2) and 399 (pre-S1) amino acids, respectively, and occur in both glycosylated and non-glycosylated forms. The hepatitis B surface antigen proteins are covalently linked to each other by intermolecular disulfide bonds between the S domains and are partially embedded in the membrane lipids, creating virus like particles that are approximately 30 nm in diameter.

The lipid composition of the HBsAg consists of phosphatidylcholine (PCs), low levels of phosphatidylethanolamine (PEs), phosphatidylinositol (PIs), lysophosphatidylcoline (LPC), lysophosphatidylethanolamine (LPE) and possible traces of free cholesterol. The secondary structure of recombinant HBsAg active substance was investigated using circular dichroism (CD) spectroscopy and has been confirmed to be predominantly alpha-helical.

2.3.2.2. Manufacture, characterisation and process controls

SciVac Ltd. (Rehovot, Israel) is the only site involved in manufacturing of the HBsAg Drug Substance. Quality control testing is conducted at SciVac Ltd., as well as at external GMP compliant laboratories.

The active substance is manufactured, packaged, stability tested and quality-control tested in accordance with good manufacturing practice (GMP).

Description of manufacturing process and process controls

The active substance manufacturing process has been adequately described. The manufacturing process is divided in upstream and downstream processes. Main steps are cell propagation, inoculation

in the bioreactor, harvest of the HBsAg-containing media, concentration of media harvest and HBsAg purification.

The *upstream manufacturing process* starts with thawing and expansion of cells from WCB for bioreactor inoculation, followed by the bioreactor growth phase and HBsAg production and harvest of the media. The cells are grown in successively larger flasks to confluence until the bioreactor is seeded. The cells are then inoculated into the bioreactor and grown until specified conditions, which favour product accumulation over cell growth, are reached. Production phase starts at predefined thresholds, during which the culture medium and bioreactor operating conditions (e.g. pH, temperature, perfusion rate, etc.) are adjusted. The harvest is collected in harvest bags.

The *downstream manufacturing process* includes HBsAg harvest clarification, up-concentration and (dia-) filtration of the media harvest, followed by two consecutive protein purification steps and viral inactivation. A terminal sterile filtration step is conducted to obtain the purified bulk active substance.

There are no reprocessing steps during active substance manufacturing process.

The active substance manufacturing process has been adequately developed and the In-Process Controls (IPCs) are considered effective to monitor and confirm process consistency. Re-use of chromatographic columns has been clearly indicated where applicable and it is found acceptable. Process parameters and in-process tests are well defined and controlled within appropriate ranges as well as in-process test controlled by action limit or acceptance criteria. Typical process and maximum hold-times are stated and are considered acceptable.

Significant variations of the total HBsAg content at the different downstream process steps are proposed by the applicant, however this is considered acceptable based on batch data generated so far. Moreover, the applicant committed to re-asses the IPC limits following the collection of data of 20 manufacturing scale purification batches tested with the new antigen quantification method by Q3 2023 (Recommendation 1).

The batch size for the active substance depends on the bioreactor productivity, as well as purification yield. The batch numbering system is adequately presented in the dossier.

The container closure system for HBsAg bulk active substance consists of type I glass bottles with a screw cap and a pouring ring.

The bottles are stored with appropriate protection against light exposure.

Adequate specifications have been proposed for the container closure system. Both primary container and closure comply with relevant standards and are commonly used for pharmaceutical products. Prior to filling, the bottles are washed and sterilized using a validated autoclave cycle.

Extractable studies on the biocontainer bags (used for holding growth medium, harvest material and concentrated harvest), on the 0.2 µm filter and on the active substance storage container were conducted by the applicant and demonstrated that there is no safety concern associated with their use. A justification for not conducting a leachable study for the active substance storage container was presented by the applicant and it was deemed acceptable, as there are no extractables identified above the analytical evaluation threshold or above levels that are considered to be harmful.

Overall, the active substance manufacturing process is considered acceptable.

Control of materials

The raw materials, components, resins, filters, membranes, and container and closures used in the manufacture of HBsAg active substance were adequately described. All raw materials used in the upstream and downstream manufacturing processes are released for use based on testing against the

relevant Pharmacopoeia specifications (compendial materials), in-house specifications (non-compendial materials) and on review of documentation provided by the vendors of the materials such as Certificate of Analysis (CoA) and, for materials of animal origin, documentation on the country of origin. The control testing applied to the raw materials is considered appropriate.

The DNA sequence encoding for the S, pre-S2, and pre-S1 HBsAg proteins was derived by recombinant DNA technology from a naturally occurring hepatitis B viral (HBV) gene. The HBsAg expression vector was used to transfect the chosen CHO cell line and stable integrants (clones with the expression vector DNA integrated into the host genome) were selected. A suitable strain was selected for further subcloning and final generation of the HBsAg-producing strain, secured in form of a pre-master cell bank, was used to prepare master and working cell banks. Therefore, the cloning strategy, the construction of the expression vector and the generation of a stably transfected CHO cell line, overexpressing the three hepatitis B envelope surface antigens, has been adequately described. The genetic stability of cell banks and the production cell line was confirmed. Cell Bank characterization for MCB and WCB is considered sufficient to ensure consistency.

The MCB and the WCB intended for commercial manufacture were prepared in 1993 and 1998, respectively, at the Rehovot site which is no longer involved in the manufacture of PreHevbri. During assessment, a major objection was raised concerning the availability of documents supporting the GMP status of the WCB used for commercial manufacturing. To demonstrate GMP compliance of the MCB and WCB#2 cell banks, the applicant presented a history of approved Marketing Authorisations involving manufacture at the site including manufacture of Bio-Hep-B (previous name for the same recombinant hepatitis B vaccine). Furthermore, a variety of documents, including GMP certificates, has been provided to substantiate GMP compliance. Additionally, the applicant has re-tested its WCB#2 according to ICH Q5A, ICH Q5D and Ph. Eur. 5.2.3 cell bank standards. All test results met the acceptance criteria of the specification and supported the safety, identity and quality of the WCB#2. Overall, the response provided sufficient evidence to support that WCB#2 can be considered GMP compliant and safe, and therefore acceptable for use in commercial manufacture.

An end of production cell bank (EoPCB) is routinely prepared from cells following termination of the bioreactor run on a periodic basis. Each batch of EoPCB is tested to show continued control of the cell line. The EoPCB testing program was updated upon request during assessment and is considered acceptable.

Protocol for the establishment of future WCBs and EoPCBs was provided and assessed as acceptable.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the HBsAg active substance manufacturing process were given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified. There are no isolated intermediates in the manufacturing process of the active substance. Hold-times for in-process materials are adequately defined.

Process validation

The active substance manufacturing process has been validated adequately.

The upstream manufacturing process validation is being supported by a retrospective continuous process validation study gathering 16 harvest batches and data has been shown that the process is reliable, robust, reproducible and adequately controlled.

For the downstream manufacturing process validation, a process performance qualification (PPQ) study has been conducted, using 3 consecutive active substance commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests were fulfilled, demonstrating that the purification process consistently produces active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

The process is maintained in a validated state by continued process verification which will be assured by continued monitoring and trending of process parameters, in-process tests, critical quality attributes (CQAs) and release data.

Shipping validation was not necessary as both active and finished product are manufactured in the same building. The life cycle studies presented support multiple uses of the chromatography columns and membrane filtration system in downstream manufacturing processes. The applicant discussed occurring deviations in the specification of the specific productivity during CHO cell incubation. It can be concluded that these deviations are not expected to have any effect on product quality.

Manufacturing process development

Development history was presented in an adequate manner covering sufficient information of all processes and all changes introduced in the active substance manufacturing process. The changes in the process were evaluated with various combined validation/comparability studies and demonstrate that there is no significant influence on the quality of the product. Data obtained throughout development for input materials, manufacturing process parameters and IPCs were discussed and CQAs are defined in line with requirements. An acceptable risk assessment of the CQAs was performed, ranking CQA based on potential clinical impact and uncertainty.

The initial development of the manufacturing process was designated as manufacturing process A. The availability of data from the initial manufacturing process development studies performed by the previous manufacturer (BTG, Israel) are limited. In 2007, the active substance and finished product manufacture were transferred from BTG to SciVac Ltd. facility located in Rehovot, Israel. The process that was transferred and validated by SciVac is denoted as Process B. Differences between Process B and Process A consist of facility related adaptations. For Process C, the purification process was replaced and implemented. This process was used to manufacture the clinical batches in support of this application, three primary stability batches and materials used to prepare the in-house reference standards. Minor optimizations concerning the viral inactivation step were implemented to the Process C (Process denoted C+), which is the current manufacturing process of HBsAg active substance. With these changes, process qualification including extended characterization testing and virus removal/inactivation validation were performed and are considered acceptable.

Characterisation

A detailed characterisation of the HBsAg active substance was presented and included analysis of primary and higher order structures, as well as characterisation of the HBsAg particles, by physicochemical and biological state-of-the-art methods. A characterization of process- and product-related impurities was also provided. Several outliers of particles with higher diameter was observed in one batch, as well as lipid content of a batch, which has been sufficiently discussed in terms of identity, cause and impact. For analysis of amino acid sequence, incomplete amino acid coverage to the reference sequence is reported. Nevertheless, the applicant presented a discussion on the potential cause impact of the incomplete coverage of the peptide mapping to the reference sequence. Although the overall coverage obtained in the historical 2007-2008 manufacturing campaigns was 88.5%, the coverage increased to 94.5% due to the additional twenty-four amino acids identified for the four active substance batches manufactured from 2017 to 2020. The justification is considered acceptable.

An analysis of the ratio of glycosylated versus non-glycosylated antigens on different batches has been provided, showing consistent glycosylation.

In summary, the characterization is considered appropriate for this type of molecule.

2.3.2.1. Specification

The HBsAg active substance release specifications are defined based on manufacturing experience, pharmacopoeial standards and statistical analysis of lot release data. In principle, release tests have been chosen adequately for this type of active substance. Parameters covered include: appearance, protein content, antigen identity, antigen content, antigen purity, relative amounts of surface antigens, pH, carbohydrate content, lipid content, residual DNA, HCP (Host Cell Protein) impurities, BSA (Bovine Serum Albumin) impurities, residual formaldehyde, bacterial endotoxins and sterility.

Comprehensive justification of specification limits for parameters stated in the active substance specification is provided. Introduction of an additional test for determining the antigen content for the active substance (in accordance to Ph. Eur. 1056), maintaining of lipid content determination as part of the release specification and tightening of several specifications (in particular for protein content, pH and Pre-S2 content) were requested during assessment.

In summary, the proposed tests panel and acceptance criteria for batch release testing are considered adequate.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

The antigenicity of HBsAg (defined as the ratio of antigenic HBsAg and total protein content in HBsAg active substance) is determined using an enzyme-linked immunosorbent assay (ELISA). For the determination of the relative amounts of HBsAg components, fluorescent labelling of the cysteine residues in the shared S protein sequence is performed. The labelled active substance is then subject to SDS-PAGE and the labelled protein components are visualized on the gel and their fluorescence intensity is measured.

Batch analysis

The applicant provided batch data (n=32), including 3 PPQ lots as well as representative historical lots, manufactured in different buildings and using different processes. All batches meet the specifications in place at the time of release, indicating consistent quality of the active substance. No apparent trend or shift in analytical results between PPQ lots and historical lots presented is identified. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The applicant has established a qualification program for primary and secondary in-house reference standards for the active substance, in compliance to the requirements set in the Ph. Eur. monograph 1056 for recombinant Hepatitis B Vaccines. As described in ICH Q6B, a tier-based strategy for establishing and maintaining HBsAg primary and secondary in-house reference materials has been developed. The HBsAg primary reference material was used to manufacture a clinical material and was fully characterized by an array of biochemical and biophysical techniques. The primary reference material may be used in routine release and stability testing. Secondary reference materials are calibrated against the primary material and are also adequately characterized. The in-house reference materials were qualified using the HBsAg active substance release specifications and additional

characterization tests. The qualification of present and future in-house primary and secondary reference standards is sufficiently described.

2.3.2.2. Stability

The HBsAg active substance stability program was established according to the ICH guidelines. The active substance shelf-life is claimed for storage at 5±3°C, in the designated container closure system. Stability data have been provided for long-term 5±3°C and accelerated 25±2°C (60±5% RH) conditions.

The analytical methods and acceptance criteria applied during stability studies are identical to the active substance release specifications, except for the limits assigned to one test parameter. In addition, it was requested during assessment that characterization tests for particle size and density need to be included in the active substance post-approval stability program, until sufficient batch data will become available.

The containers used for the active substance stability evaluation are Duran bottles, being significant smaller than the ones used for the actual manufacturing process, but otherwise identical. However, because the active substance volume to air ratio in the smaller containers used for the stability samples might not reflect the exact conditions for routine storage of commercial batches, the applicant committed to adjust the storage conditions for stability testing of the active substance as a post-approval stability commitment, which is endorsed.

Due to an observed downward trend of a test parameter when stored under long-term storage conditions, tightening of the active substance shelf-life was requested during assessment. The proposed shelf-life is supported by data generated from three primary batches, studied for at least 18 months at 5±3°C, as well as from active substance batches which were already used to manufacture finished product lots (for which stability is shown for 36 months at 5±3°C) and historical production batches supporting the changes throughout manufacturing process development. With the exception of one OOS (out-of-specification) event, all test criteria met the previously defined acceptance criteria for stability testing at 5±3°C. It can be assumed that the OOS occurred was due to an inherent characteristic of the bulk active substance with no influence on the quality.

Accelerated stability data from the studies conducted on the primary batches suggest that short-term temperature excursions up to 25°C (i.e. time out of refrigeration) that may be encountered during storage will not impact active substance quality.

Stability studies were also conducted under heat-forced degradation (45±2°C, 60±5% RH) and under light exposure stress conditions. The results from the forced degradation study demonstrate that the methods included in the stability program are stability indicating. Active substance quality attributes are affected following exposure to light, however all results were within the pre-defined acceptance criteria for the active substance stored both in primary and secondary packaging, demonstrating that they are adequate to protect the active substance from the light effect.

Adequate post-approval stability protocol information was presented and acceptable handling of any confirmed OOS was proposed.

In conclusion, the stability results indicate that the active substance is sufficiently stable and justify the proposed shelf-life when stored at a temperature of 5±3°C, in the proposed container.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The PreHevbri finished product is presented as a sterile aqueous suspension in a single-dose vial. Each single-dose of 1.0 ml contains a total of 10 µg/ml of the three included Hepatitis B antigens (S, pre-S1 and pre-S2) adsorbed on aluminum hydroxide [$Al(OH)_3$], with a final aluminum content of 0.5 mg/ml. The finished product appears turbid when mixed and forms a clear colorless supernatant and white precipitate upon settling. The vaccine is intended for intramuscular administration.

The composition of the finished product was sufficiently described and contains beside HBsAg bulk DS, sodium chloride, potassium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, aluminum hydroxide and water for injection.

All excipients are of pharmacopeial grade (Ph. Eur./USP), of non-animal origin and commonly used in parenteral formulations. There are no novel excipients used in the finished product formulation. No incompatibilities between HBsAg bulk active substance and the excipients used in the finished product formulation are reported in literature, thus no dedicated compatibility studies were deemed necessary. Moreover, the compatibility between the active substance and excipients is confirmed by the results of stability studies.

No overage of active substance to compensate for degradation during manufacture or shelf-life is required for PreHevbri finished product. The target fill volume is 1.1 ml ± 0.05 ml to ensure withdrawal of the nominal volume of 1.0 ml.

The primary packaging is a single-dose glass vial, fitted with a rubber stopper and sealed with an aluminum seal with a plastic coloured flip-off top. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The original formulation development of PreHevbri was carried out by Bio-Technology General (Israel) Ltd. (BTG), the previous marketing authorization holder. The scientific rationale for the development of PreHevbri was to include additional hepatitis B antigen components, namely pre-S1 and pre-S2, in the formulation in order to increase vaccine immunogenicity and/or optimize vaccine performance in “non-responders” to the common hepatitis B vaccines. As excipients, the initial vaccine formulation developed by BTG contained the adsorbent Aluminum phosphate ($AlPO_4$) and thiomersal as a preservative. During the subsequent formulation development, the adsorbent component has been changed to aluminum hydroxide [$Al(OH)_3$] and thiomersal has been excluded. The present vaccine formulation intended for licensure is supported by the results from major recent clinical immunogenicity and safety trials.

The applicant uses the same process designations (process A, process B, process C and process C+) for both active substance and finished product manufacturing process. Changes to the active substance manufacturing process may also have an impact on the quality attributes of the finished product and therefore the performed comparability exercises assessed both.

The most recent change to the manufacturing process (for the establishment of process version C+) affecting vaccine finished product was the implementation of a new optimized filling line and the switch to “ready to fill” vials as final vaccine containers.

Pharmaceutical development from the beginning up to present has been described adequately and changes introduced over time have been explained and justified. Altogether, the finished vaccine product development is deemed appropriate and the current finished product formulation, as well as

the equipment and materials applied, are considered rationally designed and properly implemented for the intended purpose.

2.3.3.2. Manufacture of the product and process controls

The PreHevbri Drug Product (DP) is manufactured, filled, packaged and inspected and tested at the SciVac site in Rehovot, Israel,. Some additional testing is at external GMP compliant laboratories.

This manufacturing process is considered a straightforward process and consists of the sterile filtration and mixing of the individual vaccine components in a defined order to produce the final formulated HBsAg bulk. Next, the formulated bulk is filled into the single-dose vials, which are capped and crimped immediately after filling. Visual inspection of 100% of the vials in each PreHevbri finished product batch is conducted. The manufacturing process has been described in sufficient detail in the dossier. During assessment, concerns were raised regarding several measurement excursions and the implementation of holding times, however these have been adequately addressed by the applicant and are considered resolved.

The intended batch size for each formulated bulk finished product batch has been described. Up to three HBsAg bulk active substance batches may be blended to prepare a single formulated finished product batch. The batch numbering system is adequately presented in the dossier.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate. All operational steps included in the current finished product manufacturing process have been evaluated and included in the process validation. For the validation of the current process C+, three consecutive PPQ lots have been manufactured and analysed for compliance with specification and process parameters. The three PPQ batches met all product specifications and PPQ acceptance criteria, thus confirming the robustness and consistency of the manufacturing process.

The applicant proposes a continued process verification for the finished product manufacturing process, which includes continues monitoring and trending of all CQAs, critical process parameters (CPPs) and critical material attributes (CMAs) at minimum, using control charts, process capability index (Cpk) and other statistical methods. In addition, raw materials with the potential to cause process variability will also be monitored for their impact on process performance. Periodic reports will be produced, which is considered acceptable.

Shipping validation studies have been presented. After licensure, PreHevbri finished product will be shipped from the SciVac manufacturing facility in Rehovot, Israel to EU for commercial distribution. The shipping strategy is adequately described and validated.

2.3.3.3. Product specification

The finished product release specifications comprise tests for appearance, HBsAg identity, antigen purity, potency, aluminum content, adsorption degree, volume in container, bacterial endotoxins, pH, sterility and container closure integrity.

These specifications are in line with Ph. Eur. Monograph 1056 requirements and ensure the appropriate and consistent quality of filled PreHevbri final vaccine batches. The justification of acceptance limits is considered acceptable as it is in line with Ph. Eur. requirements and reflects results from historical batches as well as from PPQ lots.

Revision of specifications was requested during assessment, in particular for introduction of an antigen purity test and introduction of an upper limit for potency testing in order to ensure continuous consistency in production, and further justification for non-inclusion of other tests. Overall, finished product acceptance criteria at release are considered acceptable.

The finished product has been characterised with respect to the presence of process related impurities, including formaldehyde, which is controlled at the level of active substance. For the presence of unadsorbed aluminum, extractables and leachables, a risk-based approach has been presented demonstrating all levels were within acceptable ranges.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. It was confirmed that the risk for any elemental impurities being present in the final vaccine is negligible.

An assessment of impurities resulting from the finished product itself during the manufacturing process or through shelf-life has not been conducted. Upon request, the applicant presented data that identified most of the product-related species and impurities. Additionally, the applicant presented long-term finished product stability data for the purity of several batches, demonstrating low levels of impurities throughout the proposed shelf-life. It can be agreed that product related impurities is low throughout the shelf-life.

During assessment, a major objection was raised to request for a risk evaluation concerning the presence of nitrosamine impurities in the finished product. In response, a risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

Analytical methods have been described in sufficient detail and non-compendial methods have been validated appropriately. Batch data provided confirm compliance of manufactured vaccine lots with the existing specifications.

Batch analysis

The applicant provided batch data (n=25), including 3 PPQ lots as well as representative historical lots, manufactured in different buildings and using different processes. All batches meet the specifications in place at the time of release, indicating consistent quality of the finished product. No apparent trend or shift in analytical results between PPQ lots and historical lots presented is identified. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

In alignment with WHO recommendations product-specific primary and secondary in-house reference standards have been established from selected production lots. These lots have been comprehensively tested for relevant quality characteristics and stability-indicating parameters and are considered appropriate to be used as reference standards for the control of the finished product lots. The requalification test program for the reference standard beyond a time period of four years (end of shelf-life), will be tested for stability indicating parameters once every three months. The qualification of present and future in-house primary and secondary reference standards was sufficiently described.

2.3.3.4. Stability of the product

The proposed finished product shelf-life is 36 months upon storage at 5±3°C. This shelf-life claim is supported by six primary stability finished product lots investigated for stability up to 48 months under long-term storage conditions (5±3°C). The active substance batches used for the manufacturing of these six finished product stability lots were manufactured using process C, but are still considered representative to the current manufacturing process C+ on the basis of the risk assessment performed by the applicant. Moreover, the six primary stability finished product lots were filled using the previous filling line and into vials procured from a different supplier which, in contrast to the vials used in the current process C+ ("ready-to-fill" vials), were washed with WFI and depyrogenated by dry heat at SciVac Ltd. prior to use. The characteristics of each vial type have been thoroughly compared and found to be almost identical. In order to exclude any adverse impact on the finished stability profile stability data collected on the finished product lots filled in previous vials are deemed suitable to support licensure of current process C+ vaccine finished product. Moreover, confirmatory stability studies of finished product lots filled in "ready-to-fill" vials, employing the three PPQ lots, are ongoing and will be completed according to the applicant's post-approval stability commitment.

The same analytical methods and acceptance criteria used for the release of finished product were used for analysis of stability samples. Upon request, the applicant has included a test for particle size at the end of shelf-life at 36 months, to the real time stability plan for the PPQ batches.

All stability results remain within pre-determined specifications during the entire stability study demonstrating that the quality attributes are maintained. Further, in support of the current shelf-life claim, heat-forced degradation studies (at 45°±2°C) and a photostability study (conducted as per ICH guideline Q1B) have been conducted demonstrating that storage of the finished product filled in glass vials and packed in an opaque carton box (secondary packaging) are sufficient to protect it from adverse effects due to light.

Accelerated stability data at 25±2°C suggest that short-term temperature excursions (i.e. time out of refrigeration) that may be encountered during shipment or during fill/finish will not adversely impact product quality.

Adequate post-approval stability protocol information is presented and acceptable handling of any confirmed OOS is proposed. Furthermore, as part of the post-approval stability commitment, one finished product batch per year will be subjected to stability testing and evaluation for continuous stability monitoring.

Based on available stability data, the shelf-life of PreHevbri finished product of 36 months and storage conditions (*Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original package, in order to protect from light*), as stated in the SmPC, are acceptable.

2.3.3.5. Adventitious agents

The PreHevbri manufacturing process contains two chromatography-steps and an intermediary chemical treatment for virus inactivation. No virus filtration step is introduced. Cell substrates and raw materials used during manufacture of PreHevbri are tested using validated methods according to the applicant's internal policy to provide high confidence that extraneous agents are not present in the final product. The adventitious agent testing of the MCB, WCBs and EoPCB is considered acceptable.

Upon request, the applicant has provided additional justification regarding retroviral clearance, together with a risk assessment including a calculation of the estimated number per dose of retroviral particles (potentially originating from the CHO cells). Moreover, reverse transcriptase (RT) activity is monitored routinely during the active substance manufacturing purification process, while a reduced

hold-time for the concentrated harvest was introduced to prevent an aging process (which was shown to reduce the purification process performance). It was concluded that the risk of the presence of retroviral particles in the final product is therefore considered to be sufficiently mitigated.

No animal derived materials are used in the manufacturing process of the active substance and finished product, with the exception of Fetal Bovine Serum (FBS), used for cell cultivation, and Trypsin-EDTA, used during the early stages of the upstream process for detachment of cells. Trypsin-EDTA is sourced from porcine (considered as a non TSE-relevant animal species) and is further subject to gamma irradiation at levels shown to provide significant inactivation of viruses and mycoplasma. FBS is sourced from Australia, which is a country considered to be free from Transmissible Spongiform Encephalopathies (TSEs) affecting animals, including Bovine Spongiform Encephalopathy (BSE) and scrapie. Upon receipt at SciVac, FBS lots are tested as part of release process according to relevant monographs. In summary, the risk for TSE contamination is considered to be low for all raw materials used in production, cell line development, including the storage of the cell banks and raw material testing. Nevertheless, the applicant committed to implement a virus inactivation step for the FBS used for cell cultivation in routine commercial manufacturing by Q2 2023 (Recommendation 2).

2.3.3.6. GMO

N/A

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the PreHevbri active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the evaluation procedure, two major objections were raised, and have been resolved throughout the procedure, the details of which are summarized below.

The first major objection was raised to request for a risk evaluation concerning the presence of nitrosamine impurities in the finished product. The requested risk evaluation has been provided by the applicant and it is therefore accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product.

A second major objection was raised later during the assessment, due to the unavailability of GMP certificates for the manufacturer employed in the preparation of MCB (1993) and WCB (1998) intended for commercial manufacture of PreHevbri, but which is no longer involved. As a response, the applicant has presented a history of approved medicinal products involving manufacture at that site, which includes manufacturing of a recombinant growth factor in which cell banks are use, as well as Bio-Hep-B (previous name for the same recombinant hepatitis B vaccine), to demonstrate GMP compliance of the MCB and WCB#2 cell banks. Furthermore, a variety of documents, including GMP certificates, has been provided to substantiate GMP compliance. Additionally, the applicant has re-tested its WCB#2 according to ICH Q5A, ICH Q5D, and Ph. Eur. 5.2.3 cell bank. All test results met the acceptance criteria of the specification and supported the safety, identity, and quality of the WCB#2. Overall, the response provided sufficient evidence to support that WCB#2 can be considered GMP compliant and safe, and therefore acceptable for use in commercial manufacture.

The requested risk assessment regarding possible retroviral contamination resulted in a negligible risk of having one infectious retrovirus particle in a dose, based on infection assay and TEM analyses calculations. Moreover, two recommendations have been agreed by the applicant in relation to the

revision of IPC limits applied during active substance downstream manufacturing process and implementation of a virus inactivation step for the FBS used for cell cultivation.

At the time of the CHMP opinion, there were no unresolved quality issues having impact on the Benefit/Risk ratio of the product.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The applicant is requested to re-asses the IPC limits following the collection of data of 20 manufacturing scale purification batches tested with the new antigen quantification method by Q3 2023.
2. The applicant is requested to implement a virus inactivation step for the FBS used for cell cultivation in routine commercial manufacturing by Q2 2023.

2.4. Non-clinical aspects

2.4.1. Introduction

The non-clinical development of PreHevbri comprises a series of single-dose and repeat-dose toxicity studies, a developmental and reproductive toxicity (DART) study, and pharmacology studies. Assessment of the immunogenicity was additionally done as part of repeat-dose toxicity and DART studies. Only the DART study was carried out under GLP regulations. Earlier studies used the previous vaccine formulation ($AlPO_4$, with thiomersal) and the remaining studies used the current vaccine formulation ($Al(OH)_3$, without thiomersal).

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The primary pharmacodynamics studies have assessed the immunogenicity of individual anti-genic components of PreHevbri in Balb/C as well as in B10/S and B10/M mice, known to be less responsive to the S antigen. These studies were designed to determine anti-HBs humoral response to PreHevbri, in comparison with the yeast-derived recombinant HBV vaccines following i.p. administration. The suitability of rodent species for these studies was supported by their responsiveness to HBsAg.

In the original study conducted using the previous formulation ($AlPO_4$, with thiomersal), the immunogenicity of PreHevbri was established in Balb/C mice showing dose-dependent seroconversion

(at anti-HBs titer of ≥ 10 mIU/mL), with 100% at dose of 0.81 µg HBsAg after i.p. administration on a prime-boost schedule (a 30 days interval). Superior anti-HBs levels for PreHevbri versus a yeast derived hepatitis B vaccine was also evidenced. Similarly superior seroconversion response of PreHevbri to two other yeast derived hepatitis B vaccines was further shown in B10/S mice and B10/M mice.

Subsequently, the ability of the current formulation of PreHevbri to induce a strong immune response was established in another study in Balb/C mice that were dosed i.p. on Day 0 and Day 21. In this study, adjuvanted PreHevbri was found to elicit stronger responses than unadjuvanted PreHevbri or a yeast derived hepatitis B vaccine after one dose. One month after the second dose, adjuvanted PreHevbri produced 100% of seroconversion rate that was almost three times the seroconversion rate noted in unadjuvanted PreHevbri (37.5%). Thus, the benefit of the $Al(OH)_3$ adjuvant in PreHevbri formulation was evidenced.

In addition, immunogenicity of the current vaccine formulation has also been demonstrated in rats as part of a repeat dose toxicity study and the DART study, after IM route of administration. In the repeated dose toxicity study, 100% and 70% seroconversion were observed for the 10 µg and 2 µg HBsAg dose level, respectively, when administered IM on a 3-dose schedule (Days 0, 14 and 28). The anti-HBs titers were 10-fold higher in the group vaccinated with 10 µg than for the group vaccinated with 2 µg HBsAg. In the DART study, female Sprague-Dawley rats immunized IM with PreHevbri (10 µg of HBsAg and 250 µg of Al(OH)3), on 30 and 15 days prior to mating and on GD 4 and 15, developed robust immuno-logical response in all animals receiving PreHevbri. This anti-HBs response persisted through the gestation and post-partum period, No anti-HBs were detected in the animals in the control groups administered placebo or placebo/adjuvant. Measurement of the anti-HBs levels in foetuses and offspring of mothers receiving PreHevbri showed that the circulating anti-HBs were transferred in utero.

2.4.2.2. Secondary pharmacodynamic studies

These studies were not performed for PreHevbri. This was considered acceptable by the CHMP.

2.4.2.3. Safety pharmacology programme

These studies were not performed for PreHevbri. This was considered acceptable by the CHMP.

2.4.2.4. Pharmacodynamic drug interactions

These studies were not performed for PreHevbri. This was considered acceptable by the CHMP.

2.4.3. Pharmacokinetics

Pharmacokinetic studies were not performed with PreHevbri. This was considered acceptable by the CHMP.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

A single-dose toxicity study was performed in rats to evaluate acute toxic effect of the old vaccine formulation. After IM injection with 5 µg HBsAg in the presence of $AlPO_4$, animals were observed for 72 hours. There were no vaccine-related effects on survival, clinical signs, body weight, clinical chemistry parameters, organ weight, and gross pathology and histopathology of selected organs.

2.4.4.2. Repeat dose toxicity

Two repeat-dose toxicity studies were performed in rats to evaluate systemic adverse effects and local tolerance, one (IBR 9100.008) using the current vaccine formulation and the other (Weizmann Report 1991) using the old vaccine formulation.

IBR 9100.008

This study, denoted as the main study, was conducted in order to evaluate the current vaccine formulation intended for marketing ($Al(OH)_3$, without thiomersal). Although considered a non-GLP study, this study was noted to be performed in accordance with GLP principles, based on an audit of the animal unit and histology laboratory facilities, including the storage, handling and labelling procedures, as well as a review of study records and documentation and internal SOPs.

In this study, three groups of Wistar rats were dosed IM on Days 0, 14 and 28 with 0.5mL of PreHevbri (2 or 10 µg HBsAg per animal), or $Al(OH)_3$ adjuvant alone, and were observed for signs of toxicity for 8 weeks. Animals were sacrificed 2 days after the last dose (= 4-week time point) or at 8 weeks following recovery.

No mortality was observed in the study. There were no related effects on clinical signs, body weights, clinical chemistry or organ weights. Changes in haematologic parameters were limited to leukocytosis in individual animals in each group, which was considered related to the adjuvant. There were no vaccine-related adverse gross or microscopic pathologic findings observed at terminal necropsy other than isolated incidence of slight discrete lymphoid hyperplasia in the spleens and lymph nodes of the vaccine treated rats, which represented an expected immunostimulatory property of the vaccine. The analysis of the injection site at four weeks showed essentially a mononuclear cell infiltration with signs of myodegeneration and depositions of $Al(OH)_3$ in all groups. These observations are commonly made after aluminum adjuvant injection. At eight weeks, the injection sites demonstrated focal and discrete mononuclear cell infiltration with small $Al(OH)_3$ deposition.

Weizmann Report 1991

This study was performed early in the product's development. The study consisted of once daily IM dosing of CD-1 rats for 14 days with the previous vaccine formulation ($AlPO_4$, with thiomersal), at 0.04, 0.2 or 2 µg of HBsAg, $AlPO_4$ adjuvant, or saline. There were no mortality and no related effects on clinical signs, haematology and clinical chemistry, gross pathology, organ weights, and histopathology. The only observation noted was the presence of peribiliar (and a few isolated findings of interstitial) mononuclear infiltrates in the liver. This observation, considered to be typical following adjuvant injection, was detected in all groups except for the saline-treated group.

2.4.4.3. Genotoxicity

These studies were not performed for PreHevbri. This was considered acceptable by the CHMP.

2.4.4.4. Carcinogenicity

These studies were not performed for PreHevbri. This was considered acceptable by the CHMP.

2.4.4.5. Reproductive and developmental toxicity

A GLP-compliant embryo-fetal and pre/post-natal reproductive toxicity study was conducted with the current vaccine formulation of PreHevbri in female Sprague-Dawley rats. The PreHevbri dose contained 10 µg HBsAg and 250 µg of $Al(OH)_3$, delivered IM in a volume of 0.5 mL, split between two sites. Six groups of F0 rats received PreHevbri, placebo or placebo/adjuvant on 30 and 15 days prior to mating, and on gestation day (GD) 4 and GD 15 (Table 1). The study was divided into two arms: Groups 1-3 comprised the embryofetal development arm (Caesarean sectioning groups), while Groups 4-6 comprised the pre and post-natal development arm (natural delivery groups).

Parameters for evaluation during the study included viability, clinical observations, body weights, food consumption, mating, pregnancy status, and gross lesions. F0 rats were also evaluated for pregnancy rate, number of corpora lutea, live and dead foetuses, implantation sites, early and late resorptions and total resorptions, pre- and post-implantation losses, and gravid uterine weights; as well as for gestation index, the live birth index and litter size, live or dead pups.

All foetuses were sexed, weighed, and examined for external, internal or skeletal anomalies. F1 pups were evaluated for body weight, viability, survival and lactation indices, as well as for developmental performance including sensory, behavioural and functional assessments.

Blood samples for anti-HBs antibody analyses were collected from F0 dams, foetuses and F1 pups.

2.4.4.6. Local Tolerance

Local tolerance of PreHevbri given as three IM injections at two-week intervals was investigated in Wistar rats as part of the repeat-dose IM toxicity study IBR 9100.008 (see section 2.4.4.2).

2.4.4.7. Other toxicity studies

No other toxicity studies were performed for PreHevbri. This was considered acceptable by the CHMP.

2.4.5. Ecotoxicity/environmental risk assessment

PreHevbri does not contain any genetically modified organism. The ingredients are not expected to pose a risk to the environment. Therefore, in accordance with the guideline on the environmental risk assessment of medicinal products for human use "EMEA/CHMP/SWP/4447/00", no environmental risk assessment was performed.

2.4.6. Discussion on non-clinical aspects

The pharmacology studies clearly establish the immunogenicity of PreHevbri in immunized mice and rats. Regardless of the formulation evaluated, PreHevbri was found superior to yeast-derived recombinant HBV vaccines, following 2 doses of vaccines given i.p. in mice. The stronger anti-HBs antibody responses demonstrable for adjuvanted PreHevbri versus unadjuvanted PreHevbri justifies the inclusion of aluminium hydroxide in PreHevbri formulation.

The results of mice studies were generated for the i.p. route, which represents clear limitation of these studies. However, the conclusion that PreHevbri is immunogenic can be established from the rat toxicity studies, where the IM route was employed and a dose-response relationship was established.

The omission of secondary pharmacodynamic and safety pharmacology studies and of the pharmacodynamic drug interaction studies are in line with the applicable regulatory guidelines.

According to the Applicant, pharmacokinetic studies were not performed or required, as this vaccine is not considered a new vaccine (containing antigens that have been previously described in the European Pharmacopoeia (Ph. Eur.)). Moreover, its adjuvant (Al $(OH)_3$) is not novel and the intended clinical route of administration (IM) is commonly used for commercial hepatitis B vaccines. This is in accordance with relevant regulatory guidelines (CPMP/SWP/465/95, WHO 2005, WHO 2014, ICH S6). Overall, it is supported that no pharmacokinetic studies are warranted with PreHevbri.

The description of the analytical methods used in the non-clinical programme provided during assessment was sufficient. Validated assays were employed for the mouse immunogenicity study and rat DART study. The general toxicity of PreHevbri was evaluated in single-dose and repeat-dose toxicity studies in rats, however, not under the GLP conditions. According to current guidelines, pivotal toxicity studies should be conducted in compliance with GLP. The lack of GLP compliance was discussed in the Scientific Advice feedback provided by EMA in January 2019 (EMA/CHMP/SAWP/25250/2019). The Applicant provided a clear justification for the absence of GLP for the pivotal 4-week repeat-dose toxicity study in rats and potential consequences of non-compliance. The study was considered to be reliable without restrictions. In addition, the Applicant stated that further GLP compliant studies were not considered scientifically justified in light of clinical experience with the vaccine (to date over 760,000 neonates, children and adults have received the vaccine assuming that all individuals received the three-dose regimen) and are not warranted for ethical reasons (Guideline on the principles of regulatory acceptance of 3Rs)".

The CHMP considered that the main repeat-dose toxicity study did not include histology analysis of the full list of organs and tissues or assessment of reversibility of the microscopic changes in selected vital organs, and study groups were not adequately sized. Despite these limitations, the CHMP acknowledged that this main study was well documented, based on an audit of the animal unit and histology laboratory facilities, as well as a review of study records and documentation and internal SOPs. Together with availability of considerable human experience with PreHevbri, showing a safe and well-tolerated profile in varying age groups including infants, consistent with these nonclinical toxicity studies, the CHMP agreed that additional GLP-compliant repeat-dose toxicity study with PreHevbri is not necessary.

There were no studies on genotoxicity and carcinogenicity, which is in line with applicable guidelines.

A formal GLP-compliant developmental and reproductive toxicity study was performed in female rats. The suitability of rats as a model was demonstrated by collected immunogenicity data. There were no related maternal toxicities, based on mortality check, clinical observation and evaluations of the body weight, food consumption and gross pathology at necropsy. There were no related adverse effects on maternal performances, including, pregnancy rate, duration of parturition, pre and post implantation losses, gestation index, live birth index and litter size. In the natural delivery arm of the F0 generation, the gestation index was 100% in each group, and there were no related adverse effects on live or dead pups. In caesarean sectioning groups of the F0 generation, the pregnancy rate was comparable across groups and there were no total resorptions and no dams littered prior to caesarean section on GD 20.

With respect to foetal anomalies, the only findings were increased incidence of incomplete ossification of sternebrae (5-6) in foetuses from the PreHevbri group, and increased number of litters with incomplete ossification of the supra occipital bones in foetuses of the PreHevbri group, compared to the

concurrent placebo control group. The Applicant considered them of no toxicological importance, since these findings were not associated with maternal toxicities or accompanied by decreases in foetal body weight. On request, the Applicant provided historical control data of the test facility for the test species, showing markedly lower rates of incomplete ossification of sternebra and supraoccipital bones than were observed in the placebo control group of the PreHevbri DART study. The Applicant ascribed this discrepancy to use of a more sensitive scoring technique in the PreHevbri DART study. Since incomplete ossification of the sternebrae and supraoccipital bones is common in rodents after Caesarean section on GD 20, which can be caught up with time, and that PreHevbri treatment did not adversely affect the prenatal increase of body mass and the F1 generation development, the CHMP agreed that the observed incomplete ossifications of sternebrae and supraoccipital bones in the PreHevbri group are likely a transient finding.

Regarding the physical and functional development of F1 pups, no PreHevbri related adverse effects were observed. However, there was slight but statistically significant decrease in the grip strength of hind limb in F1 pups of the PreHevbri group compared to controls, for which the relevance is difficult to interpret. The Applicant provided historical control data of the test facility, which showed markedly higher values for the grip strength of female hind limbs and also a high variability.

A dedicated local tolerance study was not performed, which is acceptable, since local tolerance assessment was part of a repeat-dose toxicity study.

Overall, the non-clinical programme adequately supported the marketing authorization application for PreHevbri.

2.4.7. Conclusion on the non-clinical aspects

The CHMP considered the vaccine approvable from a non-clinical perspective.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number Country	Study Design (Phase, Randomized, Control, Blinding)	Study Objectives
DOSE-RANGING		
Original formulation ($AlPO_4$ 0.5 mg/mL with thimerosal 50 µg/mL) Bio-Hep-B (Sci-B-Vac)		
HBV-003-89 Israel	Phase 2 Randomized (1:2) Dose-ranging Open-label Primary prevention	Safety and immunogenicity Comparison of 5 µg vs. 10 µg dose level of Bio-Hep-B/Sci-B-Vac
HB-88002 T Thailand	Phase 2 Dose-ranging Open-label Primary prevention	Safety and immunogenicity Comparison of 5 µg vs. 10 µg dose levels of Bio-Hep-B/Sci-B-Vac
HB-88002 S Singapore	Phase 1 and 2 Dose-ranging Open-label Primary prevention	Safety and immunogenicity Single-dose of 20 µg dose level of Bio-Hep-B/Sci-B-Vac (Phase 1) Comparison of 5 µg and 10 µg dose levels of Bio- Hep-B/Sci-B-Vac (Phase 2)
COMPARATOR-CONTROLLED		
Current formulation ($Al(OH)_3$ 0.5 mg/mL without thimerosal) Sci-B-Vac		
Sci-B-Vac-001 (PROTECT) Canada, Europe, United States	Phase 3 Comparative Randomized (1:1) Double-blind Primary prevention	Immunogenicity and safety Comparison to Engerix-B
Sci-B-Vac-002 (CONSTANT) Canada, Europe, United States	Phase 3 Comparative Randomized (1:1:1:1) Double-blind Primary prevention	Immunogenicity and safety Comparison of Lots A, B or C of Sci-B-Vac Comparison to Engerix-B
38-13-040 Russia	Phase 3 Comparative Randomized (1:1) Double-blind Primary prevention	Safety and Immunogenicity Comparison to Engerix-B
SG-005-05 Vietnam	Phase 3 Comparative Randomized (1:1:1) Single-blind Primary prevention	Safety, tolerability, immunogenicity Sci-B-Vac (SciGen- manufactured) vs Sci-B-Vac (BTG-manufactured) Secondary comparison to Engerix-B
Previous formulation ($Al(OH)_3$ 0.5 mg/mL with thimerosal 50 µg/mL) Bio-Hep-B (Sci-B-V		
38-96-040 Israel	Phase 3 Comparative Randomized (1:1) Single-blind Primary prevention	Safety, tolerability Immunogenicity Comparison to Engerix-B
Original formulation ($AlPO_4$ 0.5 mg/mL with thimerosal 50 µg/mL) Bio-Hep-B (Sci-B-Vac		
38-92-001 Israel	Phase 2 Comparative Randomized (2:2:1) Single-blind Primary prevention	Safety, tolerability and immunogenicity Comparison of batch A vs B of Bio-Hep-B/Sci-B-Vac Comparison to Engerix-B

Study Number Country	Study Design (Phase, Randomized, Control, Blinding)	Study Objectives
HBA 9006-S Singapore	Phase 2 Comparative Randomized (1:1:1) Open-label Primary prevention	Safety and immunogenicity Comparison to two licensed comparators (Engerix-B and Hepavac II)
UNCONTROLLED		
Previous formulation ($Al(OH)_3$ 0.5 mg/mL with thimerosal 50 µg/mL) Bio-Hep-B (Sci-B-Vac)		
38-92-001 (extension) Israel	Phase 2 Open-label Single-arm "extension" of Study 38-92-001 (additional treatment group) Primary prevention	To obtain additional safety, tolerability, and immunogenicity data
OTHER		
Current formulation ($Al(OH)_3$ 0.5 mg/mL without thimerosal) Sci-B-Vac		
SciB018 Israel	Phase 4 Open-label Single-arm Primary prevention	To qualify a 10 µg lot of Sci-B-Vac as the new reference standard (SPR≥ 95%)
HBV-002* Europe, Israel	Phase 3 Comparative Randomized (2:1) Open-label In non or low responders to prior HBV vaccination	Safety, tolerability Immunogenicity Comparison to Engerix-B

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

No pharmacokinetic evaluation was performed for PreHevbri. This was considered acceptable by the CHMP.

2.5.2.2. Pharmacodynamics

Anti-HBs assay

In the two pivotal Phase 3 studies (Sci B Vac 001 and Sci B Vac 002), the anti-HBs levels were measured using the validated CE-marked (CE-0459) VITROS anti-HBs quantitative assay at a central laboratory in the US.

The immunoassay is based on measurement of chemiluminescence after antigen-antibody binding.

The immunoassay was fully validated according to ICH M10 on bioanalytical method validation, including by use of calibrators referenced to the World Health Organization (WHO) 1st International Reference Preparation of anti-hepatitis B immunoglobulin.

In the supportive legacy adult studies, a number of commercially available anti-HBs platforms were used for quantitative measurement of immune response, all of which have demonstrated good sensitivity and specificity.

Dose response studies

In order to demonstrate dose response, three dose ranging studies in adults have been provided. In total, 245 healthy subjects were enrolled. Test-substance was the original vaccine with aluminium phosphate as an adjuvant and thimerosal as preservative. The studies were conducted inIsrael, Thailand, and Singapore. They were open-label, comprising two dose regimens, 5 and 10 µg. One had a preliminary phase 1 FIH part with a dosage up to 20 µg. The endpoint in each study was to achieve seroprotection, i.e. the defined antibody-titre of 10 mIU/ml or higher. The test vaccine was administered in a three consecutive dosage regimen.

In each of the studies, seroprotection as defined was achieved in the 10µg group in each participant within seven months, whereas in the 5µg group, the percentage was marginally lower. In contrast, the peak GMT-level that was reached at month seven was in all the three studies distinctly higher in the 10µg group. That superiority is evident in the 10µg group during each of the conducted laboratory measurement at the 1, 2, 6, 7 and 12-month interval. Concomitantly, the 10µg dose regimen led faster to seroprotection.

Overall, the study results indicated a clear dose response relationship with an increased dosage of 10 versus 5µg. Furthermore, the 10µg was superior with respect to both GMT as well as seroprotection.

2.5.3. Discussion on clinical pharmacology

A pharmacokinetic evaluation was not performed, which is in line with the respective CHMP guideline CHMP/VWP/164653/2005. The pharmacodynamics evaluations were confined to three dose finding studies. They elucidated a clear relationship between the administered dosage of 5 versus 10 µg and the resulting antibody titre. The dosage of 10 µg has proven to be the most favourable under the aspect of the targeted defined immunogenic correlate of protection to achieve seroprotection (see the “Correlates of protection” outlined below).

2.5.4. Conclusions on clinical pharmacology

The CHMP considered that all aspects dealing with clinical pharmacology have been well addressed by the Applicant.

2.5.5. Clinical efficacy

Correlates of protection

Anti-HBs is the only easily measurable correlate of vaccine induced protection using serologic assays. An anti-HBs concentration of 10 mIU/mL or more measured 1 to 3 months after administration of the last dose of the primary vaccination series is considered a reliable marker of protection against infection: in vaccine immunogenicity/efficacy studies, immunocompetent persons who developed anti-HVs concentrations of 10 mIU/mL of higher after vaccination had virtually complete protection against both acute disease and chronic infection, even if subsequently, over time, anti HBs concentrations declined to less than 10 mIU/mL. Indeed, the protective efficacy of hepatitis B vaccination is related to the induction of anti- HBs antibodies, but it also involves the induction of memory-B and T cells. Therefore, vaccine-induced protection against HBV infection is defined as having an anti-HBs level of

10 mIU/mL or higher, measured 1 to 3 months after receipt of a complete and adequately administered vaccination course. In immunocompromised patients who have ongoing exposure to HVB, annual anti—HBs testing is recommended, and booster doses are required to maintain anti-HBs concentrations of 10 mIU/mL or higher .

2.5.5.1. Dose response studies

Dose response studies and their results are presented under section 2.5.2.2 Pharmacodynamics.

2.5.5.2. Main studies

To support the authorisation of PreHevbri, two Phase 3 clinical studies (Sci B Vac 001 and Sci B Vac 002) that compared PreHevbri to Engerix-B were conducted in Europe and North America to evaluate the immunogenicity, safety and manufacturing consistency of the adult 10 µg (10 µg HBsAg, $Al(OH)_3$ 0.5 mg/mL without thimerosal) 3 dose regimen of PreHevbri. The comparator chosen for these phase 3 trials, Engerix-B (20 µg HBsAg), is an approved standard-of-care HBV vaccine for the immunization of adults in Europe.

An overview of the 2 pivotal Phase 3 trials was summarized in Table 1.

Table 1 Key study design features

Study Number Country	Study Design (Phase, Randomized, Control, Blinding)	Study Objectives	Study groups Number per group (safety population) Dose Schedule	Population Mean Age (Range) Gender Ethnicity Health	Sample Size Enrolled / ITT	Year
COMPARATOR CONTROLLED						
Current formulation ($Al(OH)_3$ 0.5 mg/mL without thimerosal) Sci B Vac						
Sci-B-Vac-001 (PROTECT) Canada, Europe, United States	Phase 3 Comparative Randomized (1:1) Double-blind Primary prevention	Immunogenicity and safety Comparison to Engerix-B	Sci-B-Vac 10 µg (n=796) or Engerix-B: 20 µg (n=811) 3 doses (1 mL) IM on study days 0, 28 and 168	56.6 years (≥ 18 years) Female: 61.5% 90% Caucasian Healthy	1607/ 1607	2017-2019
Sci-B-Vac-002 (CONSTANT) Canada, Europe, United States	Phase 3 Comparative Randomized (1:1:1:1) Double-blind Primary prevention	Immunogenicity and safety Comparison of Lots A, B or C Comparison to Engerix-B	Sci-B-Vac 10 µg Lot A (n=711), Lot B (n=709), or Lot B (n=706) or Engerix-B: 20 µg (n=712) 3 doses (1 mL) IM on study days 0, 28 and 168	33.5 years (18-45 years) Female: 58% 91.5% Caucasian Healthy	2838/ 2838	2017-2019

Phase 3, Double-Blind, Randomized, Controlled Trial to Compare the Immunogenicity and Safety of a Three dose Regimen of PreHevbrito a Three-dose Regimen of Engerix-B in Adults (PROTECT)

Methods

- Study Participants

Male and female subjects, 18 years of age or older in stable health or with controlled chronic conditions who consented to participate were eligible for the study. The frailty index of subjects >65 years old was ≤3. Subjects who had received any hepatitis B virus (HBV) vaccine (licensed or experimental) previously were excluded. In addition, treatment by immunosuppressants within 30 days of enrolment, autoimmune diseases or secondary immunodeficiency disorder or primary immunodeficiency disorders were excluded.

- Treatments

Vaccine administration

Study subjects were randomized in a 1:1 ratio to receive either 3 IM injections of PreHevbri or Engerix-B. The first was administered at Study Day 0, the second at Study Day 28 (at 4 weeks), and the third at Study Day 168 (at 24 weeks).

Blood sampling

- Anti-HBs Assessments

  Immunogenicity was assessed by measurement of anti-HBs levels at baseline, and at Study Days 28, 56, 168, 196, and 336.

- Cell-mediated immunity

  A small subset of subjects participating in the laboratory sub-study also participated in an optional sub study on cell mediated immunity. Subjects consenting to the cell-mediated immunity sub-study were required to provide an additional blood sample at V1 (Day 0) and at each of the additional visits (A1, A2, A3).

Anti-HBs Assessments

Immunogenicity was assessed by measurement of anti-HBs levels at baseline, and at Study Days 28, 56, 168, 196 and 336.

- Objectives

Co-Primary:

- To demonstrate that the seroprotection rate (SPR), 4 weeks after completion of the 3-dose regimen of PreHevbri, is non-inferior to the SPR 4 weeks after completion of the 3-dose regimen of Engerix-B in adults ≥18 years old i.e., the lower bound of the 2-sided 95% confidence interval (CI) of the difference between the SPR in the PreHevbri arm minus the SPR in the Engerix-B arm, achieved 4 weeks after receiving the third vaccination, is > -5%
- To demonstrate that the SPR, 4 weeks after completion of the 3-dose regimen of PreHevbri, is superior to the SPR 4 weeks after completion of the 3-dose regimen of Engerix-B in older adults ≥45 years old ie, the lower bound of the 2-sided 95% CI of the difference between the SPR in the PreHevbri arm minus the SPR in the Engerix-B arm, achieved 4 weeks after receiving the third vaccination, is >5%

Secondary:

- To determine whether the SPR after receiving 2 vaccinations of PreHevbri, evaluated at 4 weeks and 20 weeks after receiving the second vaccination (just prior to receiving the third vaccination), is non-inferior to the SPR 4 weeks after receiving the third vaccination with Engerix-B
- To compare the safety and reactogenicity of PreHevbri and Engerix-B

Exploratory:

- To compare the geometric mean concentration (GMC) of hepatitis B surface antibody (anti-HBs), 4 weeks after receiving the first vaccination, the second vaccination and the third vaccination, 20 weeks after receiving the second vaccination (just prior to receiving the third vaccination), and 24 weeks after receiving the third vaccination with PreHevbri or Engerix-B
- To compare the SPR observed 4 weeks after receiving the first vaccination and second vaccination, 20 weeks after receiving the second vaccination (just prior to receiving the third vaccination), and 24 weeks after receiving the third vaccination with PreHevbri or Engerix-B at Study Days 28, 56, 168 and 336
- To compare the proportion of subjects who achieved anti-HBs levels ≥100 mIU/mL, as a measure of an especially robust immune response, 4 weeks after each vaccination with either PreHevbri or Engerix-B, at Study Days 28, 56, and 196, and ony Days 168 and 336
- To compare the rate of non-response 4 weeks after receiving the third vaccination with PreHevbri or Engerix B
- To compare SPR, GMC, and rate of non-response in subgroups of interest (eg, body mass index (BMI) >30 kg/m2) 4 weeks after receiving the third vaccination with PreHevbri or Engerix-B
- To compare clinical laboratory parameters relative to baseline, 1 week after each vaccination with PreHevbri or Engerix-B in a subset of subjects (at least 10% of the total number of subjects enrolled to the trial) recruited at select sites
- To assess the antibody responses against pre-S1 and pre-S2 at baseline, 4 weeks after each vaccination with PreHevbri or Engerix-B, and at Study Days 168 and 336.
- To compare the boost, relative to baseline, of cell-mediated immune responses against HBsAg, 1 week after each vaccination with either PreHevbri or Engerix-B (in a small subset of subjects recruited to an optional sub study at select sites [~n=50-75 subjects/treatment arm])

- Outcomes/endpoints

Primary Endpoint

The primary endpoint of the study was:

- SPR at Study Day 196, 4 weeks after receiving third vaccination with either PreHevbri 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.

Secondary Endpoints

The secondary endpoints of the study were:

- SPR at Study Days 56 and 168, 4 weeks and 20 weeks after receiving the second PreHevbri vaccination (just prior to receiving the third vaccination), and the SPR at Study Day 196, 4 weeks after receiving the third Engerix-B vaccination
- Number (%) of subject-reported, solicited (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 event or NOCI through Day 336
- Number (%) of subjects with abnormal vital signs, and/or physical examination findings compared to baseline

Exploratory Endpoints

The exploratory endpoints of the study were:

- GMC of anti-HBs in serum, in both study arms, at baseline and at Study Days 28, 56, and 196, 4 weeks after each vaccination with either PreHevbri 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
- Proportion of subjects achieving anti-HBs levels ≥100 mIU/mL in serum, in both study arms, at Study Days 28, 56, and 196, 4 weeks after each vaccination with either PreHevbri or Engerix-B, and at Study Days 168 and 336
- Rate of non-response (defined as the proportion of subjects not attaining anti-HBs levels ≥10 mIU/mL), at Study Day 196, 4 weeks after receiving the third vaccination with either PreHevbri or Engerix-B
- Number (%) of subjects with abnormal clinical laboratory parameters from baseline assessments at Study Days 7, 35 and 175, one week after each vaccination with either PreHevbri or Engerix-B (clinical laboratory sub-study, select sites)
- The GMC of pre-S1 and pre-S2 antibodies in serum, in both study arms, at baseline and at Study Days 28, 56, and 196, 4 weeks after each vaccination with PreHevbri or Engerix-B and at Study Days 168 and 336
- Cell-mediated immunity against HBsAg at baseline (Day 0) and at Study Days 7, 35 and 175 with either PreHevbri or Engerix-B (optional sub-study in a subset of subjects participating in the clinical laboratory sub-study)

- Sample size

A total of 1564 participants were planned to be randomised.

The study population is planned to be composed of 80% of subjects ≥45 years old and 20% of subjects 18-44 years old. The sample size calculation bases on the superiority analysis on subjects ≥ 45 years of age (H2).

Assuming a SPR of 0.81 for Engerix-B and 0.96 for PreHevbri, a minimum of 540 subjects (270 per treatment group) is needed for a 90% power to demonstrate superiority of SPR with a 5% superiority margin and a significance level of 5% (two-sided). Based on the given sample size of 540 for subjects ≥ 45 years, an additional 180 (20%) of 18-44 years old study subjects were planned to be required.

With an overall sample size of 680 the power is stated to be ≥90% to demonstrate non-inferiority if the PreHevbri SPR is 0.88, the Engerix-B SPR is 0.81, setting a two-sided alpha to be 0.05 and a non-inferiority margin to be -5%.

In order to have robust immunogenicity estimates, a total of 1564 subjects were planned to be enrolled. The total number of randomized subjects were 1607.

- Randomisation and Blinding (masking)

Patients were planned to be randomized in a 1:1 allocation to receive either 3 injections of PreHevbri or 3 injections of Engerix-B. Randomisation was stratified by study center and age (18-44 years, 45-64 years, and ≥ 65 years). Randomization and treatment assignment were managed by an Interactive Web-based Response System (IWRS).

The study was planned as a double-blind study.

- Statistical methods

Populations:

The All Enrolled Set was defined as all screened subjects who provided informed consent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study.

The ITT population is a subgroup of the All Enrolled Set, who were randomised. Subjects in the ITT population were analysed "as randomised".

The Full Analysis Set (FAS) was defined as all subjects of the All Enrolled Set who received at least one vaccination and provided at least one evaluable serum immunogenicity sample both at baseline and after baseline. Patients were analysed "as randomised".

The PP set was defined as all subjects in the FAS who (i) received all 3 vaccinations, (ii) had an evaluable serum immunogenicity sample at baseline and at the time point of interest, (iii) were sero-negative at baseline, and (iv) had no major protocol deviations leading to exclusion, which was planned to be identified prior to unblinding. Patients who received the wrong treatment were excluded from the PPS.

The Safety Set was defined as is a subgroup of the All Enrolled Set, who received at least one dose of study vaccination. Subjects were analysed as vaccinated. In case of vaccination error, subjects were analysed as "treated".

The Clinical Laboratory Sub-Study Analysis Set (SSA 1) was defined as all subjects in the All Enrolled Set who actually receive at least on dose of study vaccination and participated in the clinical laboratory sub-study.

Analysis of Primary Endpoints:

The primary analysis was performed on seroprotection rate (SPR) four weeks after completion of the three-dose regimen. Seroprotection was defined as anti-HBs levels of ≥10 mIU/mL in serum and SPR was the percentage of subjects achieving seroprotection.

The two co-primary hypotheses that were tested in hierarchical order were defined as follows:

(1) H_1: Non-inferiority of PreHevbri compared to Engerix-B four weeks after the last vaccination on the PPS for the entire study population (>= 18 Years) with non-inferiority margin of -5%.

(2) H_2: Superiority of PreHevbri compared to Engerix-B four weeks after the last vaccination on the PPS for the entire study population (>= 45 Years) with superiority margin of 5%.

For testing hypothesis H_1, non-inferiority was assessed using the PPS. Two-sided 95% confidence intervals for the difference in proportions [SPR(PreHevbri)-SPR(Engerix-B)] were conducted by Miettinen-Nurminen method. Non-inferiority was declared if the lower bound of the CI was greater than the non-inferiority margin of -5%. Sensitivity analyses were conducted on the FAS population, on patients with and without seropositive immunogenicity at baseline, and on the ITT set. Additional sensitivity analysis was performed using a Logistic Regression model by adjusting for age group.

For testing hypothesis H_2, superiority was assessed using the FAS. Two-sided 95% confidence intervals for the difference in proportions were conducted by Miettinen-Nurminen method. Superiority was declared if the lower bound of the CI was greater than 5%.

Statistical testing was performed in hierarchical order.

For immunogenicity data, missing values were considered to be missing completely at random (MCAR), i.e., not informative. Therefore, each of the co-primary immunogenicity analyses were comprised a complete case analysis only, without introducing any bias. No imputation methods were planned.

Analysis of Secondary Endpoints:

If the hypotheses of the primary analysis may be rejected the following hypotheses were planned to be tested in hierarchical order:

> H_3: Non-inferiority of PreHevbri 20 weeks after the second vaccination compared to Engerix-B four weeks after the third vaccination on the PPS for the entire study population ≥ 18 years).
>
> H_4: Non-inferiority of PreHevbri 4 weeks after the second vaccination compared to Engerix-B four weeks after the third vaccination on the PPS for the entire study population ≥ 18 years).

Non-inferiority was assessed with the same approach as for the primary hypotheses. Sensitivity analyses was performed as for the primary hypotheses.

Analysis of Exploratory Endpoints:

Exploratory immunogenicity endpoints were planned to be performed on the PPS. No adjustment for multiple testing was performed.

Adjusted estimates of geometric mean serum concentrations (GMCs) and their associated 95% CIs at Day 28, Day 56, Day 168, Day 196 and Day 336 were each planned to be determined using an analysis of covariance (ANCOVA) model with factors for treatment, age group, and a covariate for the log transformed pre-vaccination (baseline) titer. The difference in GMCs between the two

treatment groups, and associated two-sided 95% CIs were presented. All statistical analyses were planned on the logarithmically (base10) transformed values. The analyses were planned to be conducted for subjects age ≥ 18 years and for subjects age ≥ 45 years old.

Analysis of Safety Endpoints:

The analysis of the safety variables based on the Safety Set. Data of laboratory safety variables were calculated in the clinical laboratory sub-study analysis set (SSA 1). Numbers of adverse events and clinical laboratory tests were summarized using descriptive statistics.

Results

- Participant flow

A total of 1 607 subjects were randomized to PreHevbri (n=796) or Engerix-B (n=811).

- Recruitment

A total of 2.472 subjects were screened for the study, of whom 865 failed screening. Thus, 1607 subjects were randomized, including 796 subjects to the PreHevbri treatment arm and 811 subjects to the Engerix-B treatment arm. All randomized subjects received their assigned treatment.

Most subjects in both treatment arms completed study treatment as planned, including 758 (95.2%) in the PreHevbri arm and 785 (96.8%) subjects in the Engerix-B arm. Early discontinuation from treatment was reported for 38 (4.8%) in the PreHevbri arm and 26 (3.2%) subjects in the Engerix-B arm. The most common reason for treatment discontinuation, contributing to the "other" category in was lost to follow-up (1.1% PreHevbri and 1.2% Engerix-B) followed by withdrawal of consent by the subject (1.0% PreHevbri and 0.6% Engerix-B). Treatment discontinuation due to non-serious AEs or SAE was uncommon, reported in 5 (0.6%) subjects in each treatment arm.

Overall, 756 (95.0%) in the PreHevbri arm and 769 (94.8%) subjects in the Engerix-B arm completed the study.

- Conduct of the study

One amendment was issued very early in the conduct of the trial before the first subjects was enrolled. Mainly exploratory endpoints clarification and exclusion criteria were better defined in the amended protocol.

- Baseline data

Baseline data are presented in Table 2. below.

Table 2 Demographics and other baseline characteristics

Demographic Variable	Engerix-B (N=811)	PreHevbri (N=796)	Total (N=1607)
Gender, n (%)			
Male	303 (37.4)	315 (39.6)	618 (38.5)
Female	508 (62.6)	481 (60.4)	989 (61.5)
Age Category (years), n (%)			
18 - 39	88 (10.9)	84 (10.6)	172 (10.7)
40 - 49	159 (19.6)	175 (22.0)	334 (20.8)
50 - 59	181 (22.3)	170 (21.4)	351 (21.8)
60 - 69	255 (31.4)	238 (29.9)	493 (30.7)
≥70	128 (15.8)	129 (16.2)	257 (16.0)
BMI category (kg/m2), n (%)			
>30	292 (36.0)	297 (37.3)	589 (36.7)
≤ 30	519 (64.0)	499 (62.7)	1018 (63.3)
Smoking status/Tobacco use, n (%)			
Current smoker/tobacco user	113 (13.9)	104 (13.1)	217 (13.5)
Former smoker/tobacco user	224 (27.6)	203 (25.5)	427 (26.6)
Non-smoker/non-tobacco user	474 (58.4)	489 (61.4)	963 (59.9)
Diabetes status, n (%)			
Diabetic	65 (8.0)	60 (7.5)	125 (7.8)
Non-diabetic	746 (92.0)	736 (92.5)	1482 (92.2)

- Numbers analysed

The analysis populations are presented in Table 3 below.

Table 3 Analysis population

Analysis Population	Engerix-B (N=811) n (%)	PreHevbri (N=796) n (%)	Total (N=2472) n (%)
All Enrolled Set			2472
Intent-to-Treat (ITT)	811	796	1607
Full Analysis Set (FAS)	803 (99.0)	782 (98.2)	1585 (98.6)
Per Protocol Set (PPS)	729 (89.9)	718 (90.2)	1447 (90.0)
Safety Set	811 (100.0)	796 (100.0)	1607 (100.0)
Clinical Laboratory Sub-study Analysis Set (SSA1)	97 (12.0)	96 (12.1)	193 (12.0)
Sub-study Analysis Set for Cell-mediated Immunity directed against HBs (SSA2)	80 (9.9)	79 (9.9)	159 (9.9)

The subject disposition for the All Enrolled Set is summarized by treatment arm in Table 4. below.

Table 4 Subject Disposition (All Enrolled Set)

Parameter	Engerix-B n (%)	PreHevbri n (%)	Total n (%)
Screened, n			2472
Screen failure, n (%)			865 (35.0)
Randomized	811	796	1607
Dosed	811 (100.0)	796 (100.0)	1607 (100.0)
Completed treatment	785 (96.8)	758 (95.2)	1543 (96.0)
Discontinued from treatment	26 (3.2)	38 (4.8)	64 (4.0)
Primary reason for discontinuation from treatment			
Non-serious AE	3 (0.4)	3 (0.4)	6 (0.4)
Pregnancy	0	3 (0.4)	3 (0.2)
SAE	2 (0.2)	2 (0.3)	4 (0.2)
Other	21 (2.6)	30 (3.8)	51 (3.2)
Completed Study	769 (94.8)	756 (95.0)	1525 (94.9)
Withdrew prior to completing the study	42 (5.2)	40 (5.0)	82 (5.1)
Primary reason for early withdrawal from study			
Lost to follow-up	20 (2.5)	15 (1.9)	35 (2.2)
Consent withdrawal, not due to an AE	9 (1.1)	11 (1.4)	20 (1.2)
Other	3 (0.4)	6 (0.8)	9 (0.6)
Moved from the study area	3 (0.4)	2 (0.3)	5 (0.3)
Non-serious AE	3 (0.4)	0	3 (0.2)
Pregnancy	1 (0.1)	2 (0.3)	3 (0.2)
Investigator decision	1 (0.1)	1 (0.1)	2 (0.1)
Any clinically significant change in subject's medical condition	1 (0.1)	0	1 (0.1)
Major protocol violation	0	1 (0.1)	1 (0.1)
Request of regulatory agency, or Sponsor or PI	0	1 (0.1)	1 (0.1)
SAE	0	1 (0.1)	1 (0.1)
Non-compliance with protocol	1 (0.1)	0	1 (0.1)

- Outcomes and estimation

Co-Primary Immunogenicity Endpoints Sci-B-Vac-001

Non-Inferiority of PreHevbri versus Engerix-B in Subjects ≥18 Years of Age at Study Day 196

Non-inferiority of PreHevbri compared with Engerix-B was assessed in all subjects ≥18 years of age by comparing the SPR induced by PreHevbri and Engerix-B at Study Day 196, 4 weeks after receiving the third vaccination. Results for the PPS analysis are presented in Table 5 below. Non-inferiority of PreHevbri as compared with Engerix-B at Study Day 196 in subjects ≥18 years of age was demonstrated and the co-primary endpoint was met.

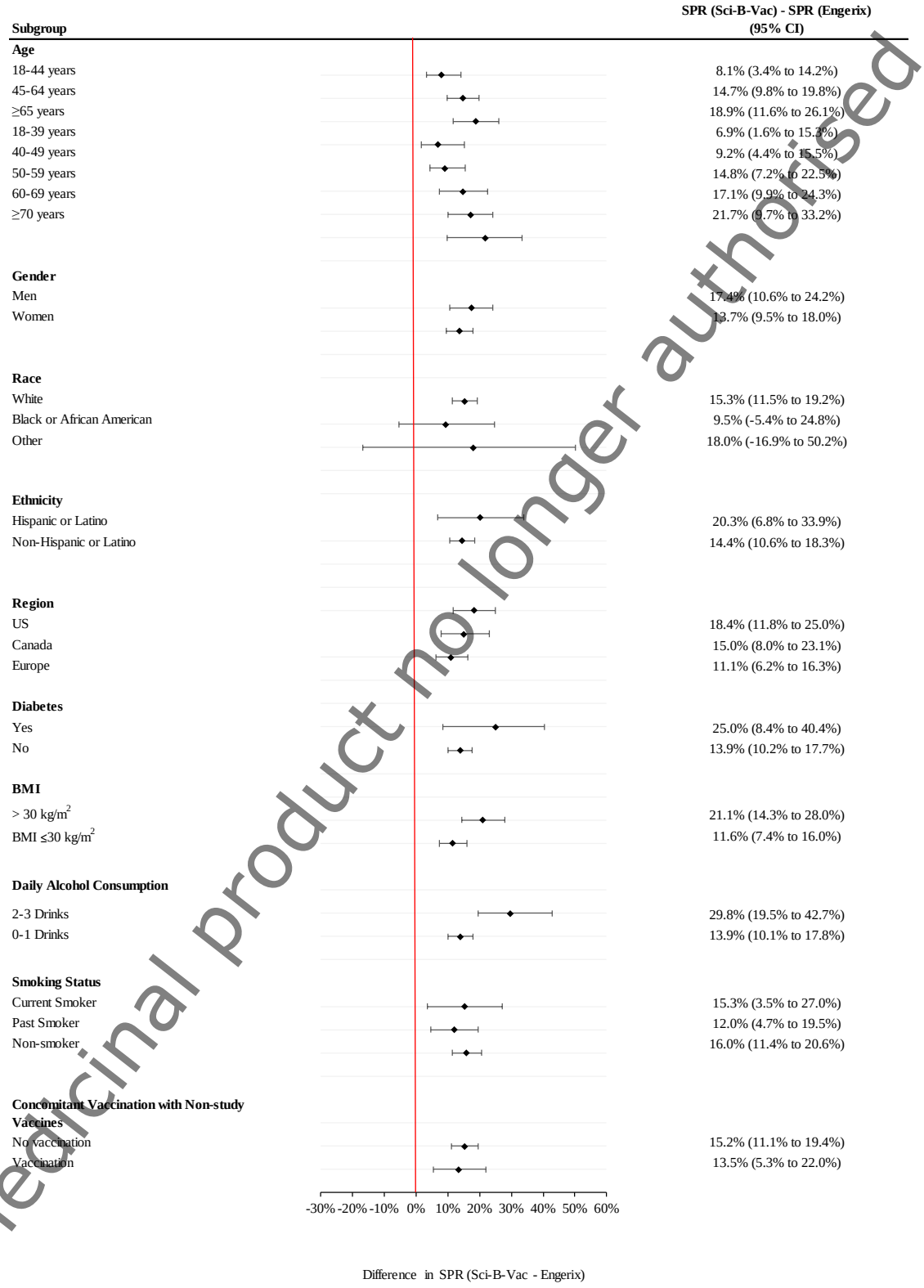
Table 5 Analysis of SPR at Study Day 196 for PreHevbri Compared to Engerix-B for Subjects ⩾18 Years of Age (Per-Protocol Set) in study Sci-B-Vac 001

Parameter	Engerix-B (N=729)	PreHevbri (N=718)
Number of subjects evaluated	723	718
Number of subjects who achieved seroprotection	553	656
Seroprotection Rate (SPR)	76.49%	91.36%
95% CI	73.22%, 79.53%	89.07%, 93.32%
Estimated difference in SPR[b]	14.88%	
95% CI	11.18%, 18.63%	

Analysis of SPR in Key Subgroups of Subjects ≥18 Years of Age in study Sci-B-Vac 001

Analyses were conducted to compare the SPR induced by PreHevbri and Engerix B within subgroups of age, sex, BMI, diabetic, smoking, alcohol consumption, concomitant receipt of any non-study licensed vaccines during the study, race, ethnicity, and country/region and to show whether SPR induced by PreHevbri or Engerix B differs by these demographic and baseline parameters or with the concomitant administration of another non-HBV licensed vaccine. Differences in SPR rates at Study Day 196 are presented in Figure 1.

Figure 1 . Subgroup Analysis of the Difference in SPR (PreHevbri – Engerix-B) at Study Day 196 for Subjects ⩾18 Years of Age (Per-Protocol Set)



Superiority of the PreHevbri versus Engerix-B in Subjects ≥45 Years of Age at Study Day 196

Superiority of PreHevbri compared with Engerix-B was assessed in subjects ≥45 years of age by comparing the SPR induced by PreHevbri and Engerix-B at Study Day 196, 4 weeks after receiving the

third vaccination; results for the FAS analysis are presented in Table 6. Both the statistical and clinical superiority of PreHevbri as compared with Engerix-B at Study Day 196 were demonstrated and the co-primary endpoint was met.

Table 6 Analysis of SPR at Study Day 196 for PreHevbri Compared to Engerix-B for Subjects ⩾45 Years of Age Excluding Those Who were Seropositive at Baseline (Full Analysis Set)

Parameter	Engerix-B (N=646)	PreHevbri (N=638)
Number of subjects evaluated	627	625
Number of subjects who achieved seroprotection	458	559
Seroprotection Rate (SPR)	73.05%	89.44%
95% CI	69.39%, 76.48%	86.76%, 91.74%
Estimated difference in SPR	16.39%	
95% CI	12.17%, 20.65%	

Among subjects ≥45 years old, the SPR was higher in the PreHevbri arm compared to the Engerix-B arm across the subgroups of age, gender, race, ethnicity, region, diabetic status, BMI, daily alcohol consumption, and smoking status. With the exception of subgroups of Black or African-American subjects, subjects in the 'other' race category, and those who were past smokers, all lower bounds of the 95% CI of the difference in SPR were above the 5% margin for clinical superiority. No asymmetry was evident from examination of the funnel plots for the difference in the SPR by region between Engerix-B and PreHevbri arm in subjects ≥45 years of age at Study Day 196.

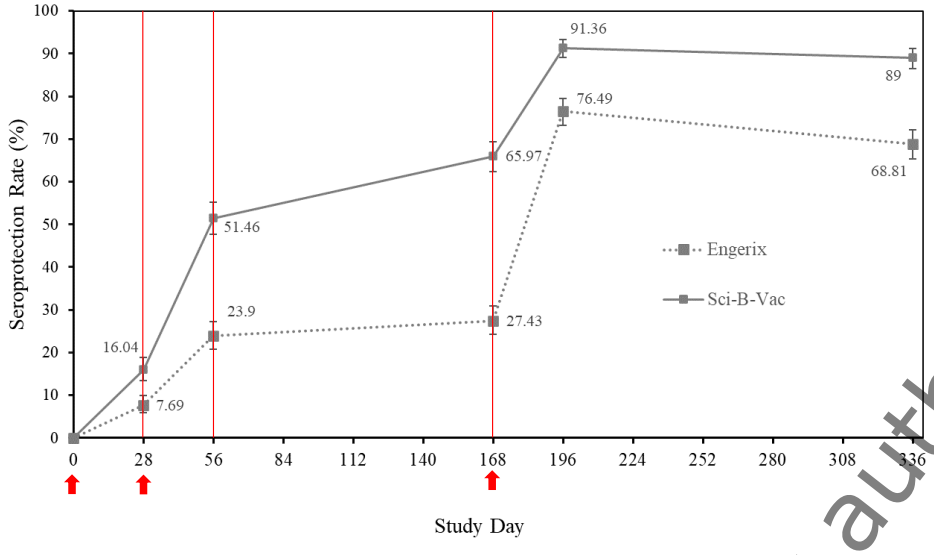
The secondary immunogenicity endpoint to demonstrate Non-Inferiority of PreHevbri at Study Day 168 (20 weeks following the second vaccination, just prior to the third vaccination) versus Engerix-B at Study Day 196 (4 weeks following the third vaccination) in Subjects ≥18 Years of Age was not met. Two doses of PreHevbri were not non-inferior to three doses of Engerix B, suggesting that the full three dose regimen of PreHevbri is required in a predominantly older population to achieve adequate levels of seroprotection.

- Exploratory analyses

<u>Seroprotection Rates at Study Days 28, 56, 168, 196, and 336 in Subjects ≥18 Years of Age</u>

In addition to comparing the SPR at Study Day 196 in the primary analysis, the SPR in both study arms was also compared at Study Days 28, 56, 168, and 336 in subjects ≥18 years of age; results for the PPS at all of these time-points are displayed graphically in Figure 2. below.

Figure 2 . Kinetics of Seroprotection in Subjects ⩾18 Years of Age (Per-Protocol Set)



Note: Solid line: PreHevbri. Dotted line: Engerix-B

Geometric Mean of Anti-HBs Titers

Table 7. presents the antibody response, as measured by GMC, at Study Days 28 (4 weeks after the first vaccination and just prior to the second vaccination), 56, 168 (prior to the third vaccination), 196 (4 weeks after the third vaccination), and 336 as well as adjusted estimates of GMCs for subjects ⩾18 years of age in the PPS.

Table 7 Analysis of HBs Antibody GMC (mIU/mL) at Study Days 28, 56, 168, 196, and 336 in Subjects ⩾18 Years of Age (Per-Protocol Set)

	Engerix-B (N=729)					PreHevbri (N=718)				
Day	28	56	168	196	336	28	56	168	196	336
n	728	728	729	723	715	717	717	717	718	709
Mean (SD)	3.24 (4.665)	5.85 (7.251)	5.82 (5.378)	192.65 (22.085)	69.24 (16.087)	4.57 (6.343)	17.25 (9.082)	27.61 (7.480)	1148.31 (15.373)	445.07 (14.128)
Median	2.12[a]	2.12[a]	2.12[a]	279.00	68.50	2.12[a]	11.27	24.00	2600.00	696.00
Q1, Q3	2.12, 2.12	2.12, 7.98	2.12, 12.00	12.70, 2580.00	2.12, 597.00	2.12, 2.12	2.12, 87.10	4.60, 123.0	224.0, 12700.0	76.5, 3810.0
Mean Adjusted GMC (SE)	3.47 (1.064)	6.75 (1.079)	6.53 (1.070)	235.43 (1.113)	83.49 (1.106)	4.80 (1.065)	19.70 (1.080)	30.84 (1.071)	1424.52 (1.114)	546.79 (1.107)
95% CI	3.07, 3.92	5.81, 7.83	5.72, 7.46	190.77, 290.54	68.54, 101.70	4.24, 5.42	16.93, 22.91	26.96, 35.29	1152.09, 1761.36	447.95, 667.45
Ratio (PreHevbri / Engerix-B)						1.38	2.92	4.72	6.05	6.55
95% CI of the difference						1.17, 1.63	2.38, 3.58	3.94, 5.66	4.54, 8.07	5.00, 8.57
p-value						<0.001	<0.001	<0.001	<0.001	<0.001

The difference in the adjusted GMC between the PreHevbri and Engerix-B arms was statistically significant at each analysis timepoint (p<0.001, Day x PreHevbri vs Day x Engerix-B).

Proportion of Subjects with Anti-HBs levels ⩾100 mIU/mL

A long live protection against hepatitis-B infection was predicted after 3 vaccination of hepatits-B

vaccine and an achieved anti-HBs Levels ⩾100 mIU/mL measured shortly after the vaccinations. At all timepoints the rate of subjects, who achieved the expected anti-HBs level was higher in the PreHevbri group compared to the Engerix-B group.

Rate of Non-Response at Study Day 196

The overall rate of non-responders is higher after vaccination in a 3-dose-schedule with Engerix-B compared to a 3-dose-schedule with PreHevbri. A favourable rate of non-responders (16.4 %) was shown for the age-stratum 65 years and above compared to Engerix-B (35.3%).

Revaccination data of non-responders who did not respond to a primary 3-dose vaccine series with anti-HBs concentration of ≥ 10 mIU/mL indicate that 25 % to 50 % responded to an additional vaccine dose, and 44 % to 100 % responded to a 3-dose re-vaccination series. Better response re-vaccination occurs in persons who have measurable but low [< 10 mIU/mL] levels after the initial series.

Preliminary results of the ongoing long-term persistence study

An investigator-initiated follow-up study is being conducted in Finland by one of the principal investigators of the Sci-B-Vac-001 Phase 3 study to evaluate the long-term persistence of hepatitis B surface antibodies (anti-HBs) in Sci-B-Vac-001 study subjects who achieved seroprotection (i.e. anti-HBs ≥ 10 mIU/mL) after a 3-dose regimen of PreHevbri compared to Engerix-B.

The preliminary results indicate that while the levels of anti-HBs in both the PreHevbri and Engerix-B groups demonstrated a decline in anti-HBs titers from Day 196, the mean anti-HBs titers in the PreHevbri group were 5 times higher compared to the Engerix-B group after approximately 2.5 years. After approximately 2.5 years, 11.9% of subjects that received PreHevbri have anti-HBs titers <10 mIU/mL compared to 27.6% of subjects vaccinated with Engerix-B. A much higher proportion of subjects in the PreHevbri group have retained titers > 100 mIU/mL compared to the Engerix-B group. Analyses are ongoing to identify factors associated with loss of anti-HBs titers in follow-up.

- Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8 Summary of efficacy for trial Sci-B-Vac-001

Title: A Phase 3 Double-Blind Randomized Controlled Trial to Compare the Immunogenicity and Safety of a Three-dose Regimen of PreHevbri to a Three-dose Regimen of Engerix-B in Adults (PROTECT)		
Study identifier	Sci-B-Vac-001	
Design	Randomized, double-blind, controlled, comparative study	
	Duration of main phase:	First subject enrolled: 13 December 2017 Last subject completed: 08 April 2019
	Duration of Run-in phase: Duration of Extension phase:	not applicable not applicable

Title:	A Phase 3 Double-Blind Randomized Controlled Trial to Compare the Immunogenicity and Safety of a Three-dose Regimen of PreHevbri to a Three-dose Regimen of Engerix-B in Adults (PROTECT)			
Study identifier	Sci-B-Vac-001			
Hypothesis	Non-inferiority and Superiority			
Treatments groups	PreHevbri		3 intramuscular (IM) injections of PreHevbri at Study Day 0, Study Day 28 and Study day 168.	
	Engerix-B		3 intramuscular (IM) injections of Engerix-B® at Study Day 0, Study Day 28 and Study day 168.	
Endpoints and definitions	Co-primary endpoint	SPR at Day 196 of subjects ≥ 18 years	Seroprotection rate in subjects ≥ 18 years 4 weeks after last vaccination (Day 196), ie. percentage of subjects ≥ 18 years with anti-HBs levels ⩾10 mIU/mL	
	Co-primary endpoint	SPR at Day 196 of subjects ≥ 45 years	Seroprotection rate in subjects ≥ 45 years 4 weeks after last vaccination (Day 196), ie percentage of subjects ≥ 45 years with anti-HBs levels ⩾10 mIU/mL	
	Secondary endpoint	SPR at Day 168 on Subjects ≥ 18 years	Seroprotection rate in subjects ≥ 18 years 20 weeks after second vaccination (Day 168) of PreHevbri compared to SPR at Day 196 of Engerix-B	
	Secondary endpoint	SPR at Day 56 on Subjects ≥ 18 years	Seroprotection rate in subjects ≥ 18 years 4 weeks after second vaccination (Day 56) of PreHevbri compared to SPR at Day 196 of Engerix-B	
Database lock	17 May 2019			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Per protocol set for non-inferiority comparison, ITT for superiority comparison <time point>			
Descriptive statistics and estimate variability	Treatment group		PreHevbri	Engerix-B
	Number of subject ≥ 18 years, PPS		718	729
	SPR on Day 196, n, %		656, 91.36 %	553, 76.49 %
	95% CI		(89.07%, 93.32%)	(73.22%, 79.53%)
	Number of subject ≥ 45 years, ITT		651	657
	SPR on Day 196, n, %		629, 89.51%	635, 72.76%
	95% CI		(86.84%, 91.79%)	(69.11%, 76.18%)
Effect estimate per comparison	SPR on Day 196, subjects ≥ 18 years		Comparison groups	PreHevbri– Engerix-B
			Difference in SPR	14.88%
			95% CI	(11.18%, 18.63%)
			Non-inferiority margin	- 5%

Title: A Phase 3 Double-Blind Randomized Controlled Trial to Compare the Immunogenicity and Safety of a Three-dose Regimen of PreHevbri to a Three-dose Regimen of Engerix-B in Adults (PROTECT)			
Study identifier	Sci-B-Vac-001		
	SPR on Day 196, subjects ≥ 45 years	Comparison groups	PreHevbri– Engerix-B
		Difference in SPR	16.75%
		95% CI	(12.55%, 20.98%)
		Superiority margin	5%
Notes	The primary endpoint could be met for both co-primary comparisons.		
Analysis description	Secondary analysis		
Descriptive statistics and estimate variability	Treatment group	PreHevbri	Engerix-B
	Number of ≥ 18 years, PPS	718	729
	SPR at Day 168 on Subjects ≥ 18 years, n, %	473, 65.97%	553, 76.49%
	95% CI	(62.37%, 69.44%)	(73.22%, 79.53%)
	SPR at Day 56 on Subjects ≥ 18 years, n, %	369, 51.46%	553, 76.46%
	95% CI	(47.74%, 55.18%)	(73.22%, 79.53%)
Effect estimate per comparison	SPR at Day 168 on Subjects ≥ 18 years	Comparison groups	PreHevbri– Engerix-B
		Difference in SPR	-10.52%
		95% CI	(-15.15%, -5.86%)
		Non-inferiority margin	-5%
	SPR at Day 56 on Subjects ≥ 18 years	Comparison groups	PreHevbri– Engerix-B
		Difference in SPR	-25.02%
		95% CI	(47.74%, 55.18%)
		Non-inferiority margin	-5%
Notes	The secondary endpoints are not significant.		

A Double-Blind Randomized Controlled Trial to Assess the Lot-to-lot Consistency of PreHevbri in Adults (CONSTANT)

Methods

- Study Participants

Eligible subjects were healthy men and women, 18 to 45 years who consented to participate in the study. Subjects who had previously received any hepatitis B virus vaccine (licensed or experimental) were excluded.

- Treatments

Subjects were to receive 3 intramuscular (IM) injections according to their assigned treatment. The first dose was to be administered at Study Day 0, the second at 4 weeks (at Study Day 28), and the third at 24 weeks (at Study Day 168).

Duration of treatment was 24 weeks (vaccinations at 0, 4 and 24 weeks) with at least 24 weeks of follow up for safety assessments after the third vaccination. The total study duration for each subject was up to 48 weeks.

Anti-HBs Assessments

Immunogenicity was assessed by measurement of anti-HBs titers at Study Day 0, on Study Day 168 just before the third vaccination, and 4 weeks and 24 weeks after the third vaccination on Study Day 196 and on Study Day 336, respectively.

- Objectives

Primary Objective

The primary objective of the study was to demonstrate the manufacturing equivalence, in terms of immunogenicity, of 3 independent consecutive lots of PreHevbri 4 weeks after the third vaccination.

Secondary Objectives

The secondary objectives of the study were:

- To demonstrate that the SPR 4 weeks after completion of the 3-dose regimen of PreHevbri was non-inferior to a 3-dose regimen of Engerix-B
- To assess the safety and reactogenicity of PreHevbri compared to Engerix-B

Exploratory Objectives

The exploratory objectives of the study were:

- To assess the geometric mean concentration (GMC) of hepatitis B surface antibody (anti-HBs) in serum after 2 vaccinations, just before receiving the third vaccination, and 24 weeks after the third vaccination with PreHevbri or Engerix-B, on Study Days 168 and 336, respectively
- To assess the SPR after 2 vaccinations, just before receiving the third vaccination, and 24 weeks after the third vaccination with PreHevbri or Engerix-B, on Study Days 168 and 336, respectively
- To assess the proportion of subjects achieving anti-HBs titers ≥100 mIU/mL in serum, as a measure of an especially robust immune response, on Study Days 168 and 196, just before and 4 weeks after the third vaccination with PreHevbri or Engerix-B, and on Study Day 336
- To assess the rate of non-response on Study Day 196, 4 weeks after the third vaccination with PreHevbri or Engerix-B
- To assess SPR, GMC, and rate of non-response in subgroups of interest (eg, subjects with a body mass index (BMI) > 30 kg/m2), 4 weeks after receiving the third vaccination with PreHevbri or Engerix-B

- Outcomes/endpoints

The primary endpoint of the study to determine lot to lot consistency for immune response was assessed by measuring GMC of anti HBs across the 3 lots of PreHevbri at Day 196, 4 weeks after the third vaccination, and was based on the 95% CI of the GMC ratios of all three pairwise comparisons between lots.

The secondary immunogenicity endpoint of the study was SPR at Study Day 196, 4 weeks after receiving third vaccination, with either Hepthrio or Engerix B. Seroprotection was defined as anti HBs

titers ≥10 mIU/mL in serum. Seroprotection rate was the percentage of subjects achieving seroprotection.

The exploratory immunogenicity endpoints of the study included:

- GMC of anti HBs in serum after 2 vaccinations, just before receiving the third vaccination, and 24 weeks after the third vaccination with PreHevbri or Engerix B, on Study Days 168 and 336, respectively.
- SPR after 2 vaccinations, just before receiving the third vaccination and 24 weeks after the third vaccination with PreHevbri or Engerix B, on Study Days 168 and 336, respectively.
- Proportion of subjects achieving anti HBs titers ≥100 mIU/mL in serum after 2 vaccinations, just before receiving the third vaccination, and 4 and 24 weeks after the third vaccination with PreHevbri or Engerix B on Study Days 168, 196, and 336, respectively.
- Rate of non-response on Study Day 196, 4 weeks after the third vaccination with PreHevbri or Engerix B. Rate of non-response was defined as the proportion of subjects not attaining anti HBs titers ≥10 mIU/mL in serum.

An additional exploratory analysis was performed to determine whether the SPR after two doses of PreHevbri, evaluated 20 weeks after the second vaccination (just prior to receiving the third vaccination), was non inferior to the SPR 4 weeks after receiving the third dose of Engerix B. This additional exploratory analysis was summarized for both PPS1 and PPS2 (defined below) with data from all 3 PreHevbri lots (pooled) compared to Engerix-B.

Secondary and exploratory immunogenicity analyses were conducted on PPS2 for the following key subgroups of interest: gender (male vs female), BMI (≤ 30 kg/m2 vs > 30 kg/m2), Smoking Status (current vs past or non-smoker), Daily alcohol consumption (≥4 drinks/day vs 2-3 drinks/day vs 0-1 drink/day), Non-study licensed vaccine (no vaccination vs vaccination), Race (White vs Black or African American vs Other), Ethnicity (Hispanic or Latino vs Non-Hispanic or Latino), Country/region (United States vs Canada vs Europe).

- Sample size

3200 subjects (800 per arm) were planned to be recruited. Overall, 2838 subjects were enrolled: 712 Engerix-B, 711 PreHevbri Lot A, 709 PreHevbri Lot B, 706 PreHevbri Lot C.

- Randomisation and Blinding (masking)

Patients were planned to be randomized in a 1:1:1:1 allocation to receive 3 injections of one of the PreHevbri lots or 3 injections of Engerix-B. Randomisation was stratified by study centre. Randomization and treatment assignment were managed by an Interactive Web-based Response System (IWRS).

This study was planned as a double-blind study.

- Statistical methods

Populations:

The All Enrolled Set was defined as all screened subjects who provided informed consent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study.

The Full Analysis Set (FAS) was defined as all subjects of the All Enrolled Set who received at least one vaccination and provided at least one evaluable serum immunogenicity sample both before baseline and after baseline. Patients were analysed "as randomised".

The PP set 1 was defined as all subjects in the FAS who (i) received all 3 vaccinations, (ii) had an evaluable serum immunogenicity sample at baseline and at the time point of interest, (iii) were seronegative at baseline, and (iv) had no major protocol deviations leading to exclusion, which was planned to be identified prior to unblinding. Patients with protocol violations that may have a significant impact on the immunogenicity result were excluded from the PPS (i.e., subjects enrolled who did not meet study entry criteria, subjects who did not receive the correct treatment, subjects who developed withdrawal criteria but were not withdrawn, subjects who received a prohibited concomitant medication). Subjects were analysed "as randomised".

The PPS2 was defined as all subjects in PPS1, but excluding those who attended study visits outside the following window: V3/Day 168 (+/- 28 days), V4/Day 196 (-7/+14 days).

The Safety Set was defined as is a subgroup of the All Enrolled Set, who received at least one dose of study vaccination.

The Sub-Study analysis set (SSA) was defined as all subjects in the All Enrolled Set who actually receive at least one dose of study vaccination and participated in the clinical laboratory sub-study.

Primary Analysis:

The primary analysis was performed on the geometric mean concentration (GMC) of anti-HBs 4 weeks after the third injection (primary endpoint). The PPS1 and PPS2 were used for the primary analysis.

One primary hypothesis, consisting of three pairwise comparisons, was planned to be tested:

(1) H_1: GMC of anti-HBs 4 weeks after the third injection for all pairwise comparisons (lot A vs B, lot B vs C, lot A vs C) are outside a margin of [0.67, 1.5] (i.e., equivalence margin).

For testing hypothesis H_1, two-sided 95% confidence intervals of the GMC ratios were conducted using ANCOVA with a factor for vaccine lot group, and a covariate for the log transformed pre-vaccination (baseline) titer. Equivalence was demonstrated if the 95% CI lie within the equivalence margin of [0.67, 1.5]. Manufacturing equivalence (lot-to-lot consistency) was shown if all three pairwise comparisons were shown to be equivalent. All statistical analyses were planned to be performed on the logarithmically (base 10) transformed values. Individual titers below the detection limit were set to half the limit. Data from centers were planned to be pooled. Missing values were not planned to be imputed (complete case analysis).

Sensitivity analysis was conducted by performing the primary analysis on the FAS, with and without seropositive patients at baseline.

Secondary analysis:

If the primary hypothesis test was successful, the secondary hypothesis may be tested:

H_2: Non-inferiority of SPR 4 weeks after completion of the three-dose regimen of PreHevbri compared to Engerix-B. Seroprotection was defined as anti-HBs levels ≥ 10mIU/mL in serum. Seroprotection rate (SPR) is the percentage (%) of subjects achieving seroprotection.

The non-inferiority margin was defined as -5%. A two-sided 95% confidence interval of the difference between the SPR in the PreHevbri arm minus the SPR in the Engerix-B arm was calculated using the Miettinen and Nurminen method. Missing values were not planned to be imputed. The secondary analysis was planned to be performed on the PPS2.

Sensitivity analysis were planned to be performed on the FAS, with and without patients who were seropositive at baseline.

Analysis of Exploratory Endpoints:

Exploratory immunogenicity endpoints were planned to be performed on the PPS2. No adjustment for multiple testing was planned.

Each of the exploratory endpoints defined in the protocol were summarized for each PreHevbri lot separately, as well as for the difference between each PreHevbri lot. Analysis of GMC endpoints were used the same methods as described for the primary endpoint. For binary data, proportions and two-sided 95% CIs were planned to be reported. The difference in proportions and two-sided 95% CIs, were calculated using the Miettinen and Nurminen method.

Additionally, each of the exploratory endpoints will be summarized with data from all 3 lots of PreHevbripooled together. Summaries were presented for PreHevbri, Engerix-B and for the treatment difference. Adjusted estimates of geometric mean serum concentrations (GMCs) and their associated 95% CIs were planned to be determined using an analysis of covariance (ANCOVA) model with factors for treatment group, and a covariate for the log transformed pre-vaccination (baseline) titer. The ratio in GMCs between treatment groups (GMC of anti-HBs in PreHevbri / GMC of anti-HBs in Engerix-B), and their associated two-sided 95% CIs were planned to be presented. For binary data, proportions and two-sided 95% CIs were reported. The difference in proportions and two-sided 95% CIs, were calculated using the Miettinen and Nurminen method.

Analysis of Safety Endpoints:

The analysis of laboratory variables was based on SSA. The analysis of the rest safety variables will be based on the Safety Set. Data from each PreHevbri lot were presented both individually as well as pooled together, while data from Engerix-B were presented separately.

Results

- Participant flow

4,452 subjects were screened. At total of 2,838 subjects were randomized to Engerix (n= 712) or to Lot A (n=711), Lot B (n=709) or Lot C (n=706) of PreHevbri. At baseline, a higher proportion (57.8%) of subjects were females and most subjects (91.5%) were white. The median age ranged from 34 to 36 years across the vaccine groups. Median BMI of subjects in the safety set was 25.4 kg/m2 and over 80% of subjects in each treatment group had BMI ≤30 kg/m2. Demographic and baseline characteristics were well balanced between the treatment groups.

- Conduct of the study

3 Amendments were approved for the conduct of the study.

- Baseline data

Baseline data are presented in Table 9. below.

Table 9 Demographics and other baseline characteristics

Demographic Variable	Engerix-B (N=712)	PreHevbri				Total (N=2836)
		Pooled (N=2124)	Lot A (N=711)	Lot B (N=708)	Lot C (N=705)	
Gender, n (%)						
Male	291 (40.9)	907 (42.7)	303 (42.6)	313 (44.2)	291 (41.3)	1198 (42.2)
Female	421 (59.1)	1217 (57.3)	408 (57.4)	395 (55.8)	414 (58.7)	1638 (57.8)
Race, n (%)						

Demographic Variable	Engerix-B (N=712)	PreHevbri				Total (N=2836)
		Pooled (N=2124)	Lot A (N=711)	Lot B (N=708)	Lot C (N=705)	
White	654 (91.9)	1941 (91.4)	650 (91.4)	641 (90.5)	650 (92.2)	2595 (91.5)
Asian	9 (1.3)	37 (1.7)	9 (1.3)	15 (2.1)	13 (1.8)	46 (1.6)
Black or African American	38 (5.3)	123 (5.8)	46 (6.5)	43 (6.1)	34 (4.8)	161 (5.7)
American Indian or Alaska Native	2 (0.3)	6 (0.3)	2 (0.3)	1 (0.1)	3 (0.4)	8 (0.3)
Other	9 (1.3)	17 (0.8)	4 (0.6)	8 (1.1)	5 (0.7)	26 (0.9)
Ethnicity, n (%)						
Hispanic or Latino	74 (10.4)	195 (9.2)	64 (9.0)	70 (9.9)	61 (8.7)	269 (9.5)
Non-Hispanic or Latino	636 (89.3)	1924 (90.6)	643 (90.4)	638 (90.1)	643 (91.2)	2560 (90.3)
Not collected per local guidelines	2 (0.3)	5 (0.2)	4 (0.6)	0	1 (0.1)	7 (0.2)
Age at informed consent (years)						
Mean (SD)	33.4 (8.10)	33.5 (7.97)	33.8 (7.96)	32.9 (8.00)	33.9 (7.91)	33.5 (8.00)
Median	35.0	35.0	36.0	34.0	36.0	35.0
Min, Max	18, 45	18, 45	18, 45	18, 45	18, 45	18, 45
Weight (kg)						
Mean (SD)	75.00 (14.389)	76.16 (14.942)	76.12 (15.102)	76.23 (14.765)	76.14 (14.978)	75.87 (14.812)
Median	73.95	75.00	75.00	75.00	75.20	74.90
Min, Max	42.4, 119.4	32.2, 135.0	42.0, 135.0	45.6, 125.0	32.2, 126.1	32.2, 135.0
BMI (kg/m^2)						
Mean (SD)	25.69 (4.103)	25.88 (4.118)	25.92 (4.215)	25.75 (3.968)	25.97 (4.170)	25.83 (4.114)
Median	24.97	25.55	25.68	25.37	25.73	25.43
Min, Max	16.3, 34.9	13.9, 34.9	16.1, 34.9	16.3, 34.9	13.9, 34.9	13.9, 34.9
BMI Category, n (%)						
≤30 kg/m^2	595 (83.6)	1737 (81.8)	576 (81.0)	591 (83.5)	570 (80.9)	2332 (82.2)
>30 kg/m^2	117 (16.4)	387 (18.2)	135 (19.0)	117 (16.5)	135 (19.1)	504 (17.8)
Smoking status/Tobacco use, n (%)						
Current smoker/tobacco user	136 (19.1)	406 (19.1)	139 (19.5)	142 (20.1)	125 (17.7)	542 (19.1)
Former smoker/tobacco user	141 (19.8)	404 (19.0)	137 (19.3)	131 (18.5)	136 (19.3)	545 (19.2)

Demographic Variable	Engerix-B (N=712)	PreHevbri				Total (N=2836)
		Pooled (N=2124)	Lot A (N=711)	Lot B (N=708)	Lot C (N=705)	
Non-smoker/non tobacco user	435 (61.1)	1313 (61.8)	435 (61.2)	435 (61.4)	443 (62.8)	1748 (61.6)
Average Daily Alcohol Consumption, n (%)						
0-1 drink/day	653 (91.7)	1992 (93.8)	673 (94.7)	660 (93.2)	659 (93.5)	2645 (93.3)
2-3 drinks/day	54 (7.6)	120 (5.6)	32 (4.5)	45 (6.4)	43 (6.1)	174 (6.1)
≥ 4 drinks/day	5 (0.7)	12 (0.6)	6 (0.8)	3 (0.4)	3 (0.4)	17 (0.6)
Country/Region, n (%)						
United States	188 (26.4)	562 (26.5)	191 (26.9)	186 (26.3)	185 (26.2)	750 (26.4)
Canada	31 (4.4)	90 (4.2)	31 (4.4)	29 (4.1)	30 (4.3)	121 (4.3)
Europe	493 (69.2)	1472 (69.3)	489 (68.8)	493 (69.6)	490 (69.5)	1965 (69.3)

- Numbers analysed

The FAS included 2640 subjects who received at least 1 vaccination and had at least baseline and 1 post baseline immunogenicity assessment: 673 in the Engerix-B group, 650 in the Lot A PreHevbri group, 661 in the Lot B PreHevbri group and 656 in the Lot C PreHevbri group.

The PPS1, which included all subjects in the FAS who received all 3 vaccinations, had at least baseline and 1 post-baseline immunogenicity assessment (at the timepoint of interest), were seronegative at baseline, and had no major protocol deviations leading to exclusion comprised 2,511 subjects, including 642 subjects in the Engerix-B group, 620 subjects in the Lot A PreHevbri group, 622 subjects in the Lot B PreHevbri group and 627 in the Lot C PreHevbri group.

The PPS2, which included all subjects in the PPS1 except those who attended study visits 3 and 4 outside of the defined windows (V3/Day 168 [+/- 28 days], V4/Day 196 [-7/+14 days]), comprised ,2381 subjects, including 603 subjects in the Engerix-B group, 590 subjects in the Lot A PreHevbri group, 591 subjects in the Lot B PreHevbri group, and 597 in the Lot C PreHevbri group.

- Outcomes and estimation

Primary Immunogenicity Endpoint: Lot-to-Lot Consistency of PreHevbri

The primary endpoint of the study was lot-to-lot consistency for immune response, as measured by GMC of anti-HBs across the 3 independent, consecutively-manufactured lots of PreHevbri at Day 196 (Lots A, B, and C), i.e. 4 weeks after the third vaccination. The results for PPS1 are presented in Table 10. below. Lot-to-Lot consistency was demonstrated as the 2-sided 95% CIs for the GMC ratios between lots were within the pre-specified margin of [0.67, 1.5] and therefore, the primary endpoint of the study was met.

Table 10 Geometric Mean Concentration of Anti-HBs at Day 196 for Lot-to-Lot Consistency (Per Protocol Set 1)

Statistic	PreHevbri Lot A (N=620)	PreHevbr iLot B (N=622)	PreHevbri Lot C (N=627)
Number of subjects evaluated	611	610	619
Mean (SD)	5883.93 (5.423)	4824.06 (6.293)	5505.98 (5.975)
Median	12200.00	10700.00	12000.00
Min, Max	2.1, 20000.0	2.1, 20000.0	2.1, 20000.0
Mean adjusted GMC (SE)	5882.25 (1.074)	4821.65 (1.074)	5569.89 (1.074)
95% CI	5112.43, 6767.99	4190.10, 5548.39	4844.63, 6403.73
Adjusted 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)		

Analysis of lot-to-lot consistency based on PPS2 shown in Table 11. below.

Table 11 Geometric mean concentration (GMC) of anti-HBsAG antibody and GMC ratio at Day 196 for lot-to-lot consistency (Per Protocol Set 2)

GMC (mIU/mL)	Sci-B-Vac Lot A (N=590)	Sci-B-Vac Lot B (N=591)	Sci-B-Vac Lot C (N=597)
GMC			
n	582	582	589
Mean	5979.52	4855.28	5553.23
SD	5.404	5.983	5.928
Median	12250.00	10450.00	12100.00
Minimum, Maximum	2.1, 20000.0	2.1, 20000.0	2.1, 20000.0
Q1, Q3	3500.00, 20000.00	2190.00, 20000.00	2690.00, 20000.00
Adjusted GMC	5977.80	4852.86	5557.54
Adjusted Standard Error of GMC	1.075	1.075	1.075
Adjusted 95% CI of GMC	5183.73, 6893.52	4208.17, 5596.31	4823.20, 6403.68
Vaccine Comparison vs. Lot A			
Unadjusted GMC Ratio	---	0.81	0.93
Unadjusted 95% CI of GMC Ratio	---	0.66, 0.99	0.76, 1.14
Adjusted GMC Ratio	---	0.81	0.93
Adjusted 95% CI of GMC Ratio	---	0.66, 0.99	0.76, 1.14
Vaccine Comparison vs. Lot B			
Unadjusted GMC Ratio	---	---	1.14
Unadjusted 95% CI of GMC Ratio	---	---	0.94, 1.40
Adjusted GMC Ratio	---	---	1.15
Adjusted 95% CI of GMC Ratio	---	---	0.94, 1.40

Note: Sci-B-Vac = PreHevbri

Although, the 2-sided 95% CIs of the anti-HBs GMC ratio between Lot A and C and between Lots B and C were within the pre-specified margin of [0.67, 1.5]; the 95% CIs for the pairwise comparison of Lots A and B [0.66, 0.99] were not within this pre-defined interval.

Results for the FAS analysis (including and excluding subjects who were seropositive at baseline) were consistent with the PPS1 analysis.

Secondary Immunogenicity Endpoint: Non-Inferiority of PreHevbri versus Engerix-B at Day 196

Non-inferiority of PreHevbri compared with Engerix-B was assessed by comparing the SPR induced by PreHevbri and Engerix-B at Study Day 196, 4 weeks after receiving the third vaccination. Data from the 3 lots of PreHevbri were pooled for this analysis. Results based on PPS2 are provided in Table 12. below. The lower bound of the 95% CI of the difference in SPR was 2.9%, which was greater than the preset margin of 5%. As such, non-inferiority of PreHevbri as compared with Engerix-B at Day 196 was demonstrated and the secondary endpoint was met.

Table 12 . Analysis of Seroprotection Rate, 4 Weeks after the Third Vaccination – Day 196 for PreHevbri Compared to Day 196 for Engerix-B (Per Protocol Set 2) in study Sci-B-Vac 002

Parameter	Engerix-B (N=603)	Pooled PreHevbri (N=1778)
Number of subjects evaluated	592	1753
Number of subjects that achieved seroprotection	561	1740
Seroprotection Rate (SPR)	94.76%	99.26%
95% CI	92.65%, 96.41%	98.74%, 99.60%
Estimated difference in SPR	4.49%	
95% CI	2.90%, 6.63%	

Results for the FAS analysis (including and excluding subjects who were seropositive at baseline) were consistent with the PPS2 analysis. Excluding subjects who were seropositive at baseline, the SPR in FAS was 99.1% in pooled PreHevbri group and 94.5% in the Engerix-B group at Day 196. The difference in SPR (PreHevbri minus Engerix-B) was 4.6% (95% CI: 3.04%, 6.67%). Results for the ITT analysis were also similar.

Seroprotection rates at Study Day 196 from the subgroup analysis are tabulated in Table 13. below and differences in the SPR between pooled PreHevbri and Engerix-B groups are displayed in Figure 3.

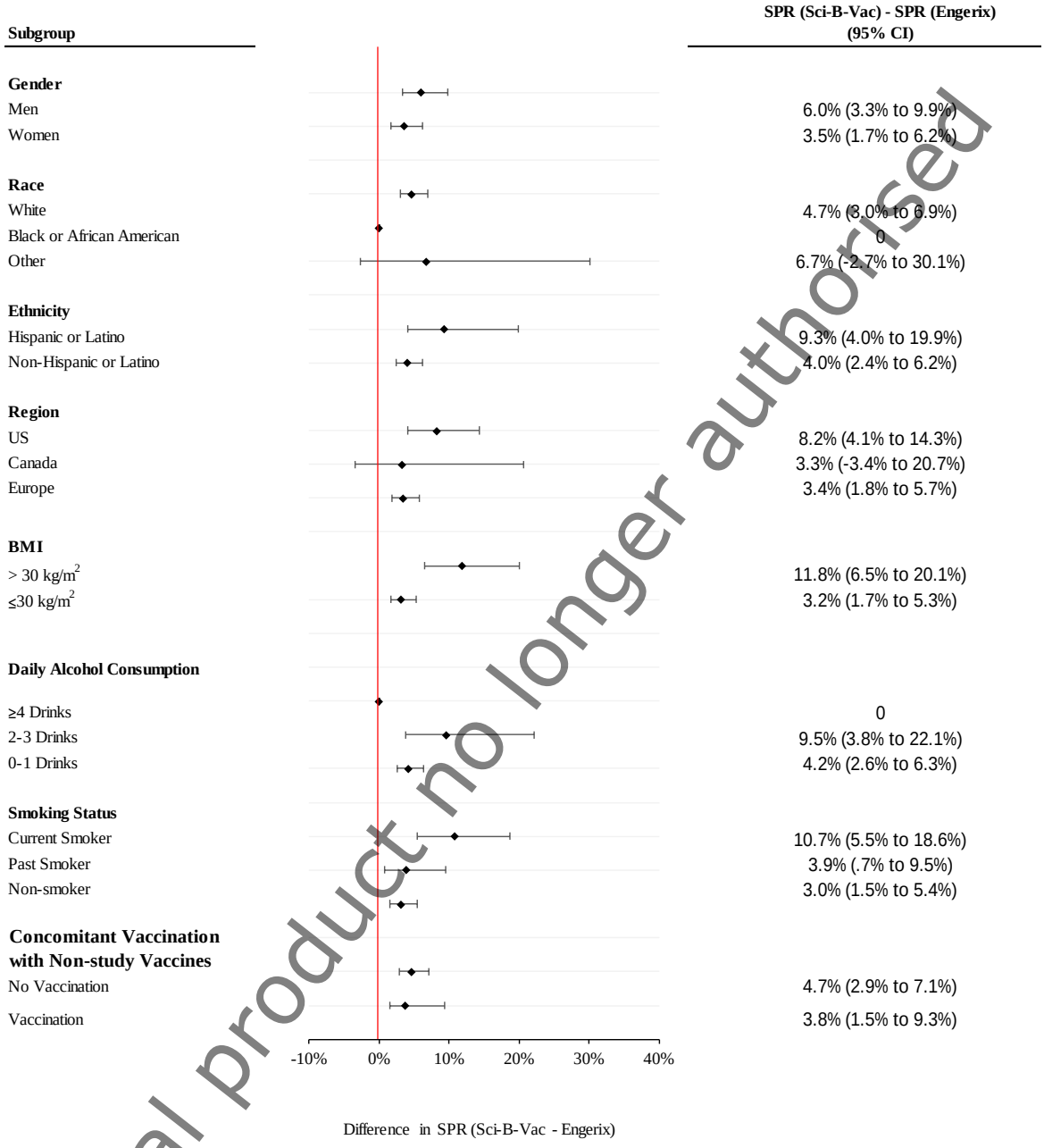
Table 13 . Seroprotection Rate of PreHevbri Compared to Engerix-B at Study Day 196 by Subgroup (Per-Protocol Set 2)

	Engerix-B			Pooled PreHevbri		
Subgroup	Subjects who Achieved Seroprotection (n/N)	SPR	95% CI	Subjects who Achieved Seroprotection (n/N)	SPR	95% CI
Gender						
Men	225/241	93.36%	89.44%, 96.16%	732/737	99.32%	98.42%, 99.78%
Women	336/351	95.73%	93.05%, 97.59%	1008/1016	99.21%	98.45%, 99.66%
Race						
White	520/550	94.55%	92.30%, 96.29%	1618/1631	99.20%	98.64%, 99.57%
Black or African American	27/27	100.00%	87.23%, 100.00%	82/82	100.00%	95.60%, 100.00%
Other	14/15	93.33%	68.05%, 99.83%	40/40	100.00%	91.19%, 100.00%
Ethnicity						
Hispanic or Latino	49/54	90.74%	79.70%, 96.92%	139/139	100.00%	97.38%, 100.00%
Non-Hispanic or Latino	510/536	95.15%	92.97%, 96.81%	1596/1609	99.19%	98.62%, 99.57%
Country/Region						
United States	125/138	90.58%	84.43%, 94.89%	400/405	98.77%	97.14%, 99.60%
Canada	21/22	95.45%	77.16%, 99.88%	76/77	98.70%	92.98%, 99.97%
Europe	415/432	96.06%	93.77%, 97.69%	1264/1271	99.45%	98.87%, 99.78%
BMI (kg/m^2)						
>30	80/91	87.91%	79.40%, 93.81%	314/315	99.68%	98.24%, 99.99%

Subgroup	Engerix-B			Pooled PreHevbri		
	Subjects who Achieved Seroprotection (n/N)	SPR	95% CI	Subjects who Achieved Seroprotection (n/N)	SPR	95% CI
≤30	481/501	96.01%	93.90%, 97.54%	1426/1438	99.17%	98.55%, 99.57%
Daily Alcohol Consumption						
≥4 Drinks	4/4	100.00%	39.76%, 100.00%	8/8	100.00%	63.06%, 100.00%
2-3 Drinks	38/42	90.48%	77.38%, 97.34%	103/103	100.00%	96.48%, 100.00%
0-1 Drink	519/546	95.05%	92.89%, 96.72%	1629/1642	99.21%	98.65%, 99.58%
Smoking Status						
Current Smoker	88/100	88.00%	79.98%, 93.64%	312/316	98.73%	96.79%, 99.65%
Past Smoker	113/119	94.96%	89.35%, 98.13%	342/346	98.84%	97.07%, 99.68%
Non-smoker	360/373	96.51%	94.11%, 98.13%	1085/1090	99.54%	98.93%, 99.85%
Concomitant Vaccination with Non-study Vaccines						
No Vaccination	459/486	94.44%	92.02%, 96.31%	1445/1458	99.11%	98.48%, 99.52%
Vaccination	102/106	96.23%	90.62%, 98.96%	295/295	100.00%	98.76%, 100.00%

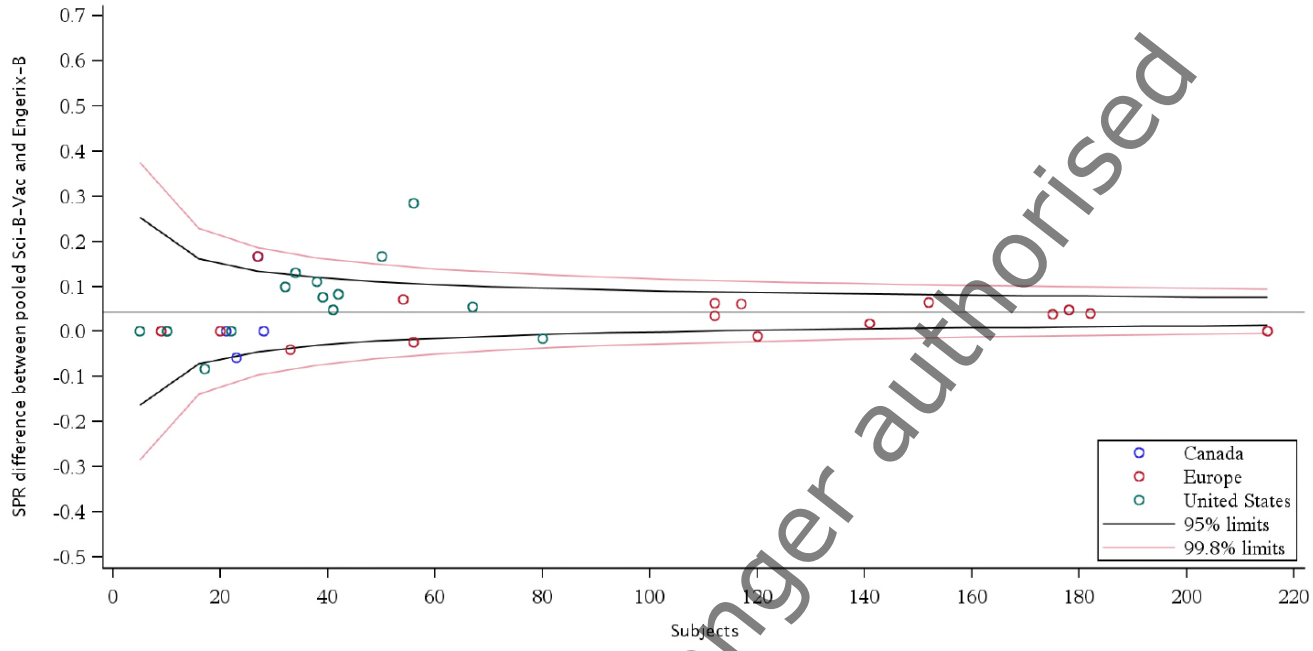
Given that only young (18-45 years) healthy subjects were enrolled to Sci-B-Vac-002 and the universally high rates of seroprotection across both PreHevbri and Engerix-B after the third vaccination, the advantage of PreHevbri over Engerix-B in subgroup-based intrinsic factors known to be associated with reduced immunogenicity (such as such as male gender, age and diabetes) was not as evident in Sci-B-Vac-002.

Figure 3. Subgroup Analysis of the Difference in SPR (PreHevbri – Engerix-B) at Study Day 196 (Per-Protocol Set 2)



No asymmetry was evident from examination of the funnel plots for the difference in the SPR between pooled PreHevbri and Engerix B groups by region at Study Day 196, as shown in Figure 4. below.

Figure 4 . Funnel plot of seroprotection rate 4 weeks after the third injection – D196 by centre (PPS2)



- Exploratory analyses

Non-Inferiority of PreHevbri at Study Day 168 versus Engerix-B at Study Day 196

Non-inferiority of PreHevbri compared with Engerix-B was assessed by comparing the SPR induced by PreHevbri at Study Day 168 (20 weeks following the second vaccination, just prior to the third vaccination) and Engerix-B at Study Day 196 (4 weeks following the third vaccination); results for the PPS2 analysis are presented in Table 14.

Table 14 Analysis of Seroprotection Rate at Day 168 for PreHevbri Compared to Day 196 for Engerix-B (Per Protocol Set 2)

Parameter	Engerix-B (N=603)	PreHevbri (N=1778)
Number of subjects evaluated	592	1775
Number of subjects that achieved seroprotection	561	1605
SPR	94.76%	90.42%
95% CI	92.65%, 96.41%	88.96%, 91.75%
Estimated difference in SPR	-4.34%	
95% CI	-6.48%, -1.90%	

The lower limit of the 95% CI exceeded -10%, the commonly-used statistical margin of non-inferiority for vaccines (Donken, de Melker et al. 2015). The statistical criterion for non-inferiority of SPR after 2 doses of PreHevbri compared with 3 doses of Engerix-B was met in the age group of adults 18-45 years.

Seroprotection rates at Study Days 168, 196 and 336

Consistent with the SPR results at Day 196 reported above, higher SPR was noted in the pooled PreHevbri group as compared with the Engerix-B group at Day 168 and Day 336. Comparison of SPR in the pooled PreHevbri group to Engerix-B group in the PPS2 is presented in Table 15

Table 15 . Summary of Seroprotection Rate at Day 168, Day 196, and Day 336 by Treatment Group (Per Protocol Set 2)

	Engerix-B		Pooled PreHevbri		Estimated Difference in SPR[a]	
Visit	n/N	SPR	n/N	SPR		95% CI[a]
Day 168	311/603	51.58%	1605/1775	90.42%	38.85%	34.64%, 43.05%
Day 196	561/592	94.76%	1740/1753	99.26%	4.49%	2.90%, 6.63%
Day 336	536/580	92.41%	1695/1718	98.66%	6.25%	4.26%, 8.74%

The SPR was similar in PreHevbri Lots A, B and C at Day 168 (89.8% Lot A, 90.2% Lot B, 91.3% Lot C), Day 196 (99.5% Lot A, 99.3% Lot B, and 99.0% Lot C) and Day 336 (99.0% Lot A, 98.8% Lot B, 98.3% Lot C).

The higher SPR in the pooled PreHevbri group compared with Engerix-B was also noted across subgroups at Day 168 and Day 336 with always the highest estimated difference at day 168 compared to Days 196 and 336.

Geometric Mean of Anti-HBs Titers at Study Days 168, 196, and 336

Table 16. presents the anti-Hbs response, as measured by GMC, at Day 168 (20 weeks following the second vaccination and prior to the third vaccination), Day 196 (4 weeks after the third vaccination), and Day 336 as well as adjusted estimates of GMCs by treatment group and visit in PPS2. Similar patterns were seen in the analysed subgroups.

Table 16 . Geometric Mean Concentration of Anti-HBs and GMC Ratio at Day 168, Day 196, and Day 336 by Treatment Group (Per Protocol Set 2)

	Engerix-B (N=603)			Pooled PreHevbri (N=1778)		
Day	168	196	336	168	196	336
n	603	592	580	1775	1753	1718
Mean (SD)	14.99 (7.149)	1526.26 (11.768)	473.02 (11.826)	118.95 (6.622)	5443.07 (5.776)	2093.80 (6.842)
Median	11.53	2900.00	581.50	128.00	11700.00	3135.00
Q1, Q3	2.12, 51.90	333.00, 12250.00	95.65, 3640.00	33.20, 451.00	2640.00, 20000.00	632.00, 10100.00
Mean Adjusted GMC (SE)	15.05 (1.080)	1567.22 (1.084)	473.11 (1.090)	118.76 (1.046)	5442.39 (1.048)	2093.67 (1.051)
95% CI	12.95, 17.51	1338.69, 1834.75	399.57, 560.19	108.77, 129.67	4967.23, 5963.00	1897.92, 2309.60
Ratio (PreHevbri /Engerix-B)				7.89	3.47	4.43
95% CI of the difference				6.62, 9.39	2.89, 4.17	3.64, 5.38

Proportion of Subjects Achieving Anti-HBs Titers ≥100 mIU/mL

At each timepoint, the proportion of subjects who achieved anti-HBs titers ≥100 mIU/mL was higher in the pooled PreHevbri group as compared with the Engerix-B group (55.3% vs 16.6% at Day 168, 95.8% vs 86.3% at Day 196, and 92.7% vs 74.0% at Day 336).

The same pattern was seen in the sub-group analysis.

Rate of Non-response at Day 196

Rate of non-response, defined as the proportion of subjects not attaining anti-HBs titers ≥10 mIU/mL, was compared at Day 196 in the Engerix-B and pooled PreHevbri groups. The rate of non-response was lower in the pooled PreHevbri group as compared with the Engerix-B group (0.74% vs 5.24%).

- Summary of main efficacy results

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17 Summary of efficacy for trial Sci-B-Vac 002

Table 22. | Summary of efficacy Title: A Double-blind Randomized Controlled Trial to Assess the Lot to-lot Consistency of PreHevbri in Adults (CONSTANT)					
Study identifier	Sci-B-Vac-002				
Design	Randomized, double-blind, multicenter, 4-arm study				
	Duration of main phase:		First subject enrolled: 14 December 2017 Last subject completed: 08 October 2019		
	Duration of Run-in phase:		Not Applicable		
	Duration of Extension phase:		Not Applicable		
Hypothesis	Equivalence and Non-inferiority				
Treatments groups	PreHevbri Lot A		3 intramuscular (IM) injections of PreHevbri from lot A (B1291V1) at Study Day 0, Study Day 28 and Study day 168.		
	PreHevbri Lot B		3 intramuscular (IM) injections of PreHevbri from lot B (B1331V1) at Study Day 0, Study Day 28 and Study day 168.		
	PreHevbri Lot C		3 intramuscular (IM) injections of PreHevbri from lot C (B1301V1) at Study Day 0, Study Day 28 and Study day 168.		
	Pooled Sci-B-Vac		Pooled data of PreHevbri Lot A, B and C		
	Engerix-B		3 intramuscular (IM) injections of Engerix-B at Study Day 0, Study Day 28 and Study day 168.		
Endpoints and definitions	Primary endpoint	GMC of anti-HBs at Day 196	Geometric mean concentration (GMC) of anti HBsAg antibody ratios 4 weeks after the third injection (day 196)		
	Secondary endpoint	SPR at Day 196	Seroprotection rate (SPR) 4 weeks after the third injection (day 196)		
Database lock	13 Dec 2019				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	Per protocol set 1 (PPS1) and Per protocol set 2 (PPS2)				
Descriptive statistics	Treatment group	PreHevbri Lot A	PreHevbri Lot B	PreHevbri Lot C	

and estimate variability	Number of subjects (PPS1)		611	610	619
	Mean adjusted GMC (SE)		5882.25 (1.074)	4821.65 (1.074)	5569.89 (1.074)
	95% CI		(5112.43, 6767.99)	(4190.10, 5548.39)	(4844.63, 6403.73)
	Number of subjects (PPS2)		582	591	597
	Mean adjusted GMC (SE)		5977.80	4852.86	5557.54
	95% CI		(5183.73, 6893.52)	(4208.17, 5596.31)	(4823.20, 6403.68)
Effect estimate per comparison		Comparison groups	PreHevbri Lot A –PreHevbri Lot B	PreHevbri A – PreHevbriLot C	PreHevbri B – PreHevbri Lot B
	GMC of anti-HBs at Day 196, PPS1	Adjusted GMC ratio	0.82	0.94	1.14
		95% CI	(0.67, 1.00)	(0.77, 1.14)	(0.94, 1.39)
		Equivalence margin	[0.67, 1.5]	[0.67, 1.5]	[0.67, 1.5]
	GMC of anti-HBs at Day 196, PPS2	Adjusted GMC ratio	0.81	0.93	1.14
		95% CI	(0.66, 0.99)	(0.76, 1.14)	(0.94, 1.4)
		Equivalence margin	[0.67, 1.5]	[0.67, 1.5]	[0.67, 1.5]
Notes	The primary endpoint was met on the PPS1 population, but not on the PPS2 population. The mean and SE were based on the log10-transformed data, then performed back to anti-HB titer. The adjusted GMC ratios were analysed using ANCOVA while adjusted for log transformed pre-vaccination (baseline) titer.				
Analysis description	Secondary analysis				
Descriptive statistics and estimate variability	Treatment group		Pooled PreHevbri	Engerix-B	
	Number of subjects evaluated, PPS2		1778	592	
	SPR at Day 168, n, %		1740, 99.26%	561, 94.76%	
	95% CI		(98.74%, 99.60%)	(92.65%, 96.41%)	
Effect estimate per comparison			Comparison groups	Pooled PreHevbri – Engerix-B	
	SPR at Day 168		Difference in SPR	4.49%	
			95% CI	(2.90%, 6.63%)	
			Non-inferiority margin	-5%	
Notes	The secondary endpoint is significant, non-inferiority of Pooled-PreHevbri vs Engerix-B regarding SPR at Day 168 was demonstrated. Seroprotection was defined as anti-HB titers 10≥ mIU/mL in serum. The estimated difference in proportions [SPR(pooled PreHevbri) -SPR(Engerix-B)] and 2-sided 95% CIs were calculated using the Miettinen and Nurminen method.				

2.5.5.3. Clinical studies in special populations

Since PreHevbri was licenced in several countries since year 2000, a number of investigator-initiated studies have been conducted to evaluate the immunogenicity in populations that are known to respond

sub-optimally to HBV vaccination. These investigator-initiated studies included e.g. subjects with HIV (Alon 2017), ESRD (Weinstein 2004), chronic kidney disease (CKD) (Elhanan 2018) and dialysis patients (Hung 2020). The immunogenicity in these investigator-initiated studies, including studies at different doses and using different administration routes than proposed in the current MAA, support the use of Prehevbri in subjects with HIV, end-stage renal disease and patients on dialysis.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The study design of the first pivotal study Sci-B Vac 001 was planned and conducted to compare the immunogenicity of a three-dose regimen of PreHevbri to a three-dose regimen of Engerix-B as a comparator to generate immunogenicity data in older adults. Engerix-B is considered the standard of care for the prevention of hepatitis-B in Europe. The study enrolled adult subjects 18 years and older, who were randomized in a 1:1 ratio to either receive PreHevbri or Engerix.

Study Sci-B-Vac-002 was a double-blind, 4-arm, randomized study to demonstrate the manufacturing equivalence of 3 lots of the PreHevbri and to compare the immunogenicity and safety of a 3-dose regimen of PreHevbri to a 3-dose regimen of Engerix-B. Eligible subjects were healthy men and women who were 18 to 45 years of age. Subjects were randomized in a 1:1:1:1 ratio to one of three lots of PreHevbri (Lot A, Lot B, or Lot C) or to Engerix-B.

Objectives and endpoints were planned similar in both studies and are considered appropriate by the CHMP. Enrolled subjects suffered from the same spectrum of comorbidities. The age-range in the second pivotal study (Sci-B-Vac 002) was limited to 45 years. The CHMP considered that the proportion of adult non-responders is higher in individuals aged 30 years and above: there is a well-documented age-dependent decline in response rate to the currently licensed HBV vaccines. Therefore, the pivotal trial Sci-B-Vac 001 was the most important study to demonstrate a higher immune-response in older adults. 80 % of subjects enrolled were aged 40 years and above. The studies included a larger subgroup of subjects with obesity (BMI > 30 kg/m2), but a rather small subgroup of subjects with e.g. diabetes, i.e. other common factors known to be associated with impaired immune response.

The Applicant has provided only limited data from groups with reduced response to hepatitis vaccines other than older adults, such as people with kidney or liver disease, or HIV infection.

Efficacy data and additional analyses

Study Sci-B-Vac-001 had two co-primary endpoints that were tested hierarchically. The primary immunogenicity endpoint of the study was the SPR at Study Day 196, 4 weeks after receiving the third injection of either PreHevbri 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. The two co primary analyses were (1) non inferiority of PreHevbri compared to Engerix B in subjects ≥18 years old at Study Day 196 and (2) superiority of PreHevbri compared to Engerix B in subjects ≥45 years old at Study Day 196. Both co-primary endpoints were met in Study Sci-B-Vac 001. These results of non-inferiority and superiority were consistent across key subgroups, which were enrolled in this study. Key subgroups were defined by age, gender, diabetes status, BMI, daily alcohol consumption, and smoking habits. Women achieved higher seroprotection rates compared to male subjects in both treatment groups. The SPR values decreased in both vaccine-arms with increasing age, smoking, BMI above 30

and more than 1 drink per day. The CHMP considered that this phenomenon of decreased immune response is known from former hepatitis-B vaccines and that the Applicant addressed the issue by adding the key subgroups in the study design and the corresponding immunogenicity analysis.

A hierarchical testing method was used for the secondary endpoints analyses. First, non-inferiority of the SPR for PreHevbri at Study Day 168, compared to the SPR for Engerix- B at Study Day 196 was to be assessed. If that endpoint was met, then non-inferiority of PreHevbri at Study Day 56, compared to Engerix- B at Study Day 196 was to be assessed. The first secondary objective was not met. Two doses of PreHevbri were not non inferior to three doses of Engerix B, suggesting that the full three dose regimen of PreHevbri is required in a predominantly older population to achieve adequate levels of seroprotection. Only the youngest age stratum (18-44 years) developed a comparable SPR after two doses PreHevbri compared to three doses Engerix 87.2% vs 91.1%. The first secondary objective was not met and therefore, the results for the non-inferiority analysis of PreHevbri at Study Day 56, compared to Engerix B at Study Day 196 are not discussed due to hierarchical testing method.

Exploratory analysis showed that SPR in the PreHevbri arm was more than twice as high as the SPR in the Engerix-B arm at all timepoints in the first 6 months: 16.0% vs. 7.7% at Study Day 28, 51.5% vs. 23.9% at Study Day 56, and 66.0% vs. 27.4% at Study Day 168. Furthermore, significantly higher GMCs of anti-HBs were noted for PreHevbri compared with Engerix-B at all timepoints. Markedly higher anti-HBs titers were noted after the second dose of PreHevbri (Study Day 56) with GMC of 17.25 mIU/mL as compared with 5.85 mIU/mL in the Engerix B arm. Anti-HBs titers peaked at Study Day 196 in both treatment arms with higher GMCs noted in the PreHevbri arm as compared with the Engerix-B arm (1148.31 mIU/mL vs 192.65 mIU/mL).

At all timepoints, the rate of subjects who achieved the expected anti-HBs level ≥100 mIU/mL was higher in the PreHevbri group compared to the Engerix-B group. The rate of non-responders was higher in the Engerix-B arm compared to the PreHevbri arm. Overall, subjects generally responded well to PreHevbri and better than to Engerix-B, regardless of demographic and baseline factors. While increasing age is a factor associated with non-response to HBV vaccination in both vaccines, the impact of this factor is consistently lower across all age groups in the PreHevbri group compared to the Engerix-B group. These results indicate a promising treatment option in cases of insufficient immune response.

Of note, investigations to address the exploratory endpoints related to antibody responses against pre-S1 and pre-S2, as well as cell-mediated immune response against HBsAg were provided by the Applicant. Regarding anti-Pre-S1 and anti Pre-S2 antibody responses, high avidity antibody responses were induced against pre-S1 and/or pre-S2 in approximately 23% of subjects vaccinated with PreHevbri. It is possible that the response rate is higher than seen, but the lack of sensitivity of the assay may preclude its detection. Although there appears to be some degree of correlation of positive response to pre-S1 and pre-S2 with anti-HBs titers, the sample size was very limited and may limit the interpretation of the data. Despite assay variability and false positives associated with the cultured ELISpot assay to detect cell-mediated immunity results, the frequency of detectable responders and magnitude of response was greater with PreHevbri (N=80). Statistically significant between group differences were observed on Day 35 (7 days after the second vaccination with both vaccines). At this timepoint, background activity was high in both groups. However, the difference in adjusted mean frequency of IFN-γ-secreting SFU/million PBMCs was statistically significant ($p < 0.05$) and greater in PreHevbri subjects. These responses to pre-S1 and pre-S2 at Day 35 in the PreHevbri group were correlated with anti-HBs titer at Day 196. A similar, statistically significant correlation between ELISpot responses against the pre-S1, pre-S2 and S antigens at Day 175 and anti-HBs titers at Day 196 was also observed in PreHevbri subjects after 3 doses of vaccines. Notwithstanding the limited sample size (N=50), correlation of mean stimulation index of pre-S2 on Day 175 with anti-HBs Geometric Mean Titers on Day 196 was also statistically significant in the PreHevbri subjects. Further correlation

analyses demonstrated strong and statistically significant correlations between ELISpot responses to pre-S2 at Day 35 after vaccination with PreHevbri and anti-HB titers in subjects at Days 56 and 168. No such correlations to pre-S1 and pre-S2 were seen in the Engerix-B group indicating that the ELISpot response observed in this group were likely background "noise" of the assay. Despite containing half the antigen content of Engerix-B, PreHevbri is considered to induce a comparable magnitude of response to HBsAg in a similar number of subjects after the second and third doses relative to Engerix-B.

Data from investigator-led studies indicated an adequate immune response to PreHevbri (at 10 µg and 20 µg doses) in subjects with HIV, end-stage renal disease (ESRD) and patients on dialysis who were vaccine-naïve or non-responders to previous vaccinations.

The primary immunogenicity endpoint in study Sci-B-Vac 002 of lot-to-lot consistency between the 3 batches was met for the PPS1 and FAS population, but not for the PPS2 population subjects who attended study visits 3 and 4 outside of the defined windows (V3/Day 168 [+/- 28 days], V4/Day 196 [-7/+14 days]). Even though the lot-to-lot consistency could not be proven for the PPS2 population for the comparison of Lot A vs Lot B, the difference in PPS1 and PPS2 results are negligible.

The secondary immunogenicity endpoint, i.e. the demonstration of non-inferiority of PreHevbri compared with Engerix-B, was assessed by comparing the SPR (ie, percentage of subjects with anti-HBs titers ≥10 mIU/mL) induced by PreHevbri and Engerix-B at Study Day 196, 4 weeks after receiving the third vaccination. Data from the 3 lots of PreHevbri were pooled for this analysis. The pooled SPR at study day 196 in subjects in the PPS2 and FAS who received PreHevbri was 99.3 % compared to 94.8% for subjects who received Engerix-B, i.e. a difference of 4.50% (95% CI: 2.9, 6.6). Non-inferiority of PreHevbri compared to Engerix B was based on the difference in SPR and the lower bound of the 2-sided 95% CI, using a -5% margin of non-inferiority. 2.9 as the lower bound proved the non-inferiority of PreHevbri compared to Engerix-B. The SPR in the PreHevbri group was consistent across all subgroups evaluated, and a higher SPR as compared with the Engerix-B group was noted in all subgroups, with the exception of the subgroup of Black or African American subjects and the subgroup of subjects who consumed ≥4 alcoholic drinks at baseline. These subgroups of subjects achieved a 100% SPR with both Engerix-B and PreHevbri, although the sample sizes were small.

The first exploratory objective to demonstrate non-inferiority of PreHevbri compared with Engerix-B was assessed by comparing the SPR induced by PreHevbri at Study Day 168 (20 weeks following the second vaccination, just prior to the third vaccination) and Engerix-B at Study Day 196 (4 weeks following the third vaccination). The statistical criterion for non-inferiority of SPR after 2 doses of PreHevbri compared with 3 doses of Engerix-B was met in the age group of adults 18-45 years.

Higher mean GMC of anti-HBs were noted after vaccination with PreHevbri (pooled) compared to Engerix B after the second vaccination at Study Day 168 (118.95 mIU/mL vs 14.99 mIU/mL) and after the third vaccination at Study Day 196 (5443.07 mIU/mL vs 1526.26 mIU/mL). The rate of non-responders was lower in subjects who received PreHevbri compared to Engerix-B.

Overall, the substantially higher mean GMC in the PreHevbri group compared to the Engerix-B group at all measured time points is considered clinically relevant. In addition, a plot showing the distribution of anti-HBs titers (reverse cumulative distribution plot) for the PreHevbri group and the Engerix-B group was provided for each time point from both the Sci-B-Vac 001 and the Sci-B-Vac 002 study. At each timepoint, higher titers were achieved by a greater percentage of subjects in the PreHevbri group compared to the Engerix-B group in both studies. Peak titers were achieved at Day 196, 4 weeks after the third vaccination in both studies.

It was observed that GMC of anti-HBs titers in the PreHevbri group continued to be higher compared to the Engerix-B group up to day 336 (6 months after the third vaccination). The higher peak titers at Day 196 in the PreHevbri group in both studies were shown to translate into higher rates of seroprotection at one year (Day 336) at both the 10 mIU/mL and the 100 mIU/mL thresholds.

An investigator-initiated follow-up study is being conducted in Finland by one of the principal investigators of the Sci-B-Vac-001 Phase 3 study to evaluate the long-term persistence of hepatitis B surface antibodies (anti-HBs) in Sci-B-Vac-001 study subjects who achieved seroprotection (i.e. anti-HBs ≥ 10 mIU/mL) after a 3-dose regimen of PreHevbri compared to Engerix-B. With this submission, the Applicant provided persistence data up to 2.5 years after vaccination either with Engerix-B or PreHevbri. These data indicated a robust and lasting immune response, which was considered convincing by the CHMP. It was demonstrated that the level of GMTs and seroprotection rates for the PreHevbri vaccine group are higher than for the Engerix-B-group. Moreover, the proportion of subjects in the PreHevbri group that have retained titers > 100 mIU/mL is approximately two-fold compared to the Engerix-B group.

The CHMP recommended that results from this investigator-initiated follow-up study be submitted once published.

2.5.7. Conclusions on the clinical efficacy

Overall, the data from the two pivotal and several supportive studies indicated immunogenicity of PreHevbri across the age (above 18 years) as well as other key subgroups. The proposed 3-dose schedule was supported by SPRs and GMCs documented in the pivotal trials.

The efficacy profile of PreHevbri is considered to support a positive B/R balance.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Within the two pivotal studies (Sci-B-Vac-001 and Sci-B-Vac 002) a total of 2,920 subjects were exposed to PreHevbri, of whom 2,725 (93.3%) received the full 3-dose schedule. This number is regarded as adequate, in accordance with the WHO guideline (2017 “Annex 9, Guidelines on clinical evaluation of vaccines: regulatory expectations”), taking into consideration that also data from the post marketing setting are available for this vaccine and no safety concerns arouse to date. The most frequent reasons for not completing the study were “lost to follow up” (N=166), “withdrawal of consent not due to AE” (N=56), “pregnancy” (N=13) and “moved from the study area” (N=9). Withdrawal for non-serious AE was documented for 6 subjects, and due to SAEs for 3 subjects.

The studies enrolled only adult patients (≥18 years). This was considered acceptable, as the paediatric indication is not sought by the Applicant. Elderly subjects ≥65 years (N=296, 37.2% in study Sci-B-Vac-001) were included. Demographics between PreHevbri and the comparator Engerix-B in the pooled data set were well matched, except for age. The imbalance was due to study Sci-B-Vac-002, which only enrolled subjects 18-45 years of age, randomized 1:3 to either Engerix-B or PreHevbri. Thus, in the polled data set, the percentage of older subjects was lower for PreHevbri (10.1% ≥65 years of age) compared to Engerix-B (19.4%).

An additional 1,881 subjects were exposed to PreHevbri or a former formulation of the vaccine (containing thiomersal, until 1998; containing $AlPO_4$, until 1994) within other clinical studies, of which 743 subjects were vaccinated with the current formulation of PreHevbri.

In the post-marketing setting, an estimated 305,302 subjects have been vaccinated with the 10 µg dose in a 3 dose schedule since 2000.

2.5.8.2. Adverse events

In the two pivotal studies, adverse events were classified as solicited local, solicited systemic and treatment emergent adverse events, the latter including all unsolicited adverse events occurring within 28 days after each vaccination and all solicited events continuing beyond Day 7.

Solicited AEs were assessed Day 1-7 following vaccination. Unsolicited AEs were assessed through day 28 post vaccination, and serious adverse events (SAE), medically attended adverse event (MAAE) and new onset of a chronic illness (NOCI) were assessed through day 336.

Any solicited local adverse events were reported in 81.4% and 55.7% of subjects vaccinated with PreHevbri and Engerix-B, respectively. The differences between the vaccines were mainly driven by the AE of local pain (72.2% and 44.5%, respectively) and tenderness (71.2% and 44.2%, respectively). Local reactions to PreHevbri were more frequent after the first vaccination (69.8%), compared to the 2nd (61.3%) and 3rd (61.4%) vaccination.

The majority of solicited local reactions were mild to moderate. Severe solicited local AEs were reported more frequently in the PreHevbri group (2.4%) compared with the Engerix-B group (0.9%).

Both frequency and severity of solicited local reactions were higher in study Sci-B-Vac-002 compared to study Sci-B-Vac-001 for both vaccines. A higher reactogenicity of PreHevbri compared to comparator vaccines has also been observed in former trials. Concerning the higher local and to a lesser extent systemic reactogenicity for PreHevbri in this trial, the difference might be lower than the data indicate; of note, Sci-B-Vac-002 enrolled younger subjects (18-45 years of age), randomized 1:3 to either Engerix-B or PreHevbri. Thus, in the pooled data set, percentage of older subjects with less reactogenicity was lower for PreHevbri (10.1% ≥65 years of age) compared to Engerix-B (19.4%). Severe local reactions were reported in 0.6% (Sci-B-Vac-001) and 1.1% (Sci-B-Vac-001) subjects for the Engerix-B group, and for 1.3% and 2.9% for the PreHevbri group. Due to the imbalance in patient numbers in study Sci-B-Vac-002, pooled data slightly increase the differences in reactogenicity observed between the two vaccines.

Grade 4 local reactions were reported for 0.7% (N=10) subjects in the Engerix-B group and 0.5% (N=14) subjects in the PreHevbri group. The AE or either redness or swelling/ oedema were not medically confirmed, as they were not medically attended. The maximum diameter was up to 50 mm (defined as grade 1) and did not (re-)occur after previous/following vaccinations. Redness and/or swelling/ oedema were reported by less than 3% of subjects vaccinated with either Engerix-B or PreHevbri.

Solicited systemic adverse events included nausea/vomiting, diarrhoea, headache, fatigue and myalgia. Body temperature was measured and recorded daily by the subjects for 7 days after each vaccination. Solicited systemic AEs were reported after any vaccination in 54.1% and 64.7% of subjects in the Engerix-B and PreHevbri group, respectively. Similar to the local reactions but to a lesser extent, the frequency and severity of solicited systemic AEs was higher in study Sci-B-Vac-002 compared to study Sci-B-Vac-001.

The difference in the overall systemic reactogenicity was mainly due to myalgia, reported for 28.1% of subjects in the Engerix-B vaccine group and 41.7% in the PreHevbri vaccine group, respectively. For myalgia, differences between the vaccines were evident in both studies (24.3% and 34.7%, respectively in study Sci-B-Vac-001 and 32.4% and 44.4% respectively in study Sci-B-Vac-002).

Again, the pooled data further increased the difference due to the aspects discussed above for local reactogenicity.

The majority of solicited systemic AEs were mild to moderate. In the pooled data, severe solicited systemic AEs were reported in 2.8% subjects in the PreHevbri and 2.6% in Engerix-B group. Despite higher frequencies for severe systemic reactions in the Engerix-B group in Study Sci-B-Vac-001 (2.3% versus 1.6%), and 2.9% versus 3.2% in study Sci-B-Vac-002, the higher percentage for PreHevbri in the pooled data again was due to the imbalances in subjects enrolled in study Sci-B-Vac-002. Grade 4 solicited systemic reactions were reported for 3 subjects in the PreHevbri group, with one case of nausea/vomiting, headache and fatigue each.

Fever, defined as body temperature ≥38°C, was reported in 0.7% to 1.3% of subjects vaccinated within Sci-B-Vac-001 or with one of the three lots (A, B or C) in study Sci-B-Vac-002. Severe fever (39 °C to 40°C) was recorded in 0.1% of subjects in study Sci-B-Vac-001 and in 0.3% (N=2) of participants vaccinated with Lot B, and for none vaccinated with Lot A or Lot C. Fever >40°C was documented for one subject (0.1%) vaccinated with Lot C.

Treatment emergent AEs were reported at similar frequencies within each study and in the pooled data for both treatment arms. The most frequent TEAEs that were reported within 28 days of any vaccination in the PreHevbri and Engerix-B group were headache (11.0% and 10.0%), upper respiratory tract infection (8.4% and 7.6%), nasopharyngitis (4.6% and 4.8%) and fatigue (3.9% and 3.7%), respectively. Also the table presenting all TEAEs, i.e. including events that occurred with a frequency below 1%, did not reveal any meaningful imbalance with regards to the nature or frequency of TEAS.

The overall frequency of reported TEAEs decreased in both vaccine groups after successive vaccinations; subjects in the PreHevbri and Engerix-B groups reported TEAEs at 29.6% and 30.0% after vaccination 1, 21.3% and 21.9% after vaccination 2, and 21.2% and 19.4% after vaccination 3, respectively.

Unsolicited adverse events that occurred within 28 days of vaccination and lasted longer than 28 days were uncommon and similar with Engerix-B in both Sci-B-Vac-001 and Sci-B-Vac-002 pivotal studies.

Most of the TEAEs within 28 days of any vaccination were mild or moderate in severity. Grade 3 and 4 TEAEs within 28 days of any vaccination were low and reported at similar incidences in the PreHevbri and Engerix-B groups (6.4% and 6.3%, respectively).

Excluding the solicited AEs persisting beyond day 7 after any vaccination, TEAEs in 305 subjects (10.4%) in the PreHevbri group and 130 subjects (8.5%) in the Engerix-B group were deemed vaccine-related. Of those, the most frequent TEAEs for PreHevbri vs. Engerix-B were upper respiratory tract infection (1.0% vs. 0.7%), dizziness (1.0% vs. 0.5%), injection site bruising (0.8% vs. 0.6%), oropharyngeal pain (0.7% vs. 0.5%), nasopharyngitis (0.6% vs. 0.4%) and headache (0.5% vs. 0.7%). The only Grade 3 or 4 related TEAEs reported were two cases of gastroenteritis in the PreHevbri group (0.1%).

2.5.8.3. Serious adverse event/deaths/other significant events

The incidence of SAEs was slightly higher in the PreHevbri, compared with the Engerix-B vaccine group. SAEs were reported in 74 subjects (2.5%) and 24 subjects (1.6%), respectively. One SAE was assessed as related by the investigator, but not by the sponsor: viral gastroenteritis in the PreHevbri group. The sponsors´ assessment which concluded against causality was accepted and therefore the AE of viral gastroenteritis is not listed in the SmPC. None of the SAEs in the Engerix B group were considered vaccine-related.

The frequency of Medically attended solicited and unsolicited adverse events (MAAEs) was similar for PreHevbri and Engerix-B vaccinated (0.6% vs. 0.5% solicited, and 22.7% vs. 23.4% unsolicited). The most frequently reported MAAEs during the study in the PreHevbri group (with corresponding incidence in the Engerix-B group) were upper respiratory tract infection (1.5% vs. 1.3%), sinusitis (1.3% vs. 1.2%), urinary tract infection (1.2% vs. 1.6%), back pain (0.9% vs. 0.5%), and depression (0.7% both groups).

The frequency of Investigator determined New Onset of Chronic Illness Events (NOCI) was similar for PreHevbri and Engerix-B vaccinated (2% vs. 2.5%). Hypertension was the most often reported event for both groups (0.3% vs. 0.5%) and the SmPC includes information regarding hypertension with the frequency rare.

Contrary to local and systemic reactogenicity, frequency of SAEs was higher in study Sci-B-Vac-001 compared to Sci-B-Vac-002, experienced by 2.6% and 4.0% of subjects in the Engerix-B and Hebhtiro group, respectively in study Sci-B-Vac-001 compared to 0.4% and 2.0% also respectively, for study Sci-B-Vac-002. The differences in frequency were mainly due to SAEs in the SOCs of cardiac and gastrointestinal disorders, infections and neoplasms, which were reported more frequently in study Sci-B-Vac-001, i.e. the study with the older study population.

It was reported that one patient died of cardiac arrest on day 7 after first vaccination with PreHevbri. The cause of death was not related to the vaccine.

Overall, there was no specific pattern of SAEs or deaths that are suspected to be related to vaccination with PreHevbri.

2.5.8.4. Laboratory findings

A laboratory substudy was performed in 393 Sci-B-Vac subjects and 193 Engerix-B subjects. The majority of subjects had no shifts from their baseline biochemistry values or shifted to Grade 1 or 2 abnormalities.

2.5.8.5. Safety in special populations

Safety was assessed in different sub-populations based on age, gender, ethnicity, race, region (US, Canada, Europe), BMI, smoking status, alcohol intake and diabetes (yes/no).

Of all subjects enrolled, 296 subjects ≥65 years were vaccinated with PreHevbri, of whom 53 were ≥75 years of age. As for the pooled date, local and systemic solicited AEs were more frequently reported for PreHevbri compared to Engerix-B. Local reactogenicity was lower in the elderly compared to the pooled data. The most frequent local reactions pain and tenderness were reported in 55.1% and 54.7% of subjects, respectively, aged 65-74 years and 45.1% for both reactions in the 75-84 years old, compared to 72.2% and 71.1%, respectively, in the pooled date-set.

Solicited systemic events were reported at similar frequencies for the 65-74 and 75-84 years age groups (43.2% and 43.1%). This was below the overall frequency in the pooled data set of 64.7% for any systemic solicited AE.

The most frequent solicited systemic adverse event, myalgia, was reported in 27.6% in the 65-74 and 27.5 % in the 75-84 year old subgroups, compared to a frequency of 41.7% in the pooled data-set. Lower frequencies were also reported for fatigue, occurring in 24.7% and 23.5% of the 65-74 and 74 - 84 years old, respectively, compared to 37.5% in the pooled data. Similarly, headache was less frequent with 18.5% and 13.7%, also respectively for the two elderly age groups, compared to 36.3% in the pooled data.

With regards to gender, solicited AEs were more frequent in female subjects, with local AEs in the PreHevbri versus Engerix-B group at 86.5% vs. 60.5% for females and 74.4% vs. 48.1% for males, respectively. The overall rate of solicited systemic AEs was 70.7% vs. 58.8% for females and 56.5% vs. 46.8% for males, respectively. Severity grade 3 was more frequent for woman than for men.

Concerning race, solicited AEs were more frequent in White subjects. The overall rate of solicited local AEs in the PreHevbri and Engerix-B groups was 83.3% vs. 56.8% for White subjects and 55.6% vs. 35.0% for Black or African American subjects, respectively. However, pruritus was more frequently reported in Black or African American subjects receiving PreHevbri, with 16.4% compared to 11,7% in Whites. The overall rate of solicited systemic AEs in the PreHevbri and Engerix-B groups was 66.2% vs. 55.3% for White subjects and 41.8% vs. 35.9% for Black or African American subjects, respectively. White subjects reported a slightly higher incidence of SAEs than Black or African American subjects who received PreHevbri (2.6% vs. 1.6%, respectively). A similar picture was seen for Hispanics/Latinos vs. non-Hispanics, with higher frequencies of solicited AEs in the Non-Hispanic subjects. Similarly to the above, pruritus was the exception with higher frequencies reported in Hispanics after vaccination with PreHevbri, with 13.1% versus 12.1% in non-Latinos/non-Hispanics.

With regards to age, Sci-B-Vac-001 is considered a more relevant source of adverse event data in the older adults, as this study enrolled a wider population of adults across a broad age range and included adults with well-controlled chronic conditions. All 296 study participants of 65+ years that received PreHevbri were enrolled in Sci- B-Vac-001. Upon request, the Applicant submitted an integrated analysis of Sci-B-Vac-001 and Sci-B-Vac-002. A small increase in the frequency of general age-related adverse events among older PreHevbri subjects in the Sci-B-Vac-001 study was noted. These events, which include cardiac disorders, vascular disorders, hospitalization and cataracts, are not unexpected and only occurred in 2 people each in the 75–84 year-old age group. Injection site pain, as an adverse event, appeared to be more common in the 75–84 year-olds than in younger subjects, but occurred at a low absolute frequency (n=4), and again is not unexpected in older subjects due to changes in body composition. Given the low frequency of these events among older subjects, no updates to the Product Information were considered necessary. The frequency of SAEs across age groups was comparable in the Sci-B- Vac-001 study.

Non-diabetic subjects reported a higher overall rate of solicited AEs. Solicited local AEs in the PreHevbri and Engerix-B groups was 81.7% vs. 56.7% for non-diabetic subjects and 65.6% vs. 32.3% for diabetic subjects, respectively. Again, the exception is pruritus with slightly higher rates in diabetics (13.1%) versus non-diabetics (12.2%) after PreHevbri vaccination. The overall rate of solicited systemic AEs in the PreHevbri and Engerix-B groups was 65.0% vs. 55.1% for non-diabetic subjects and 52.5% vs. 30.8% for diabetic subjects, respectively.

Subjects with a BMI ≤30 reported a higher frequency of the two local solicited AEs of pain and tenderness compared to subjects with BMI>30, while the other local AEs were slightly lower. There were no differences with respect to systemic solicited AEs.

Analysing the subgroups by extrinsic factors, the overall frequency of solicited local and systemic events were similar between smokers and non-smokers and alcohol consumption.

Several groups of patients and special populations were not included in the pivotal trials. Additional information was requested for pregnant and lactating women, patients with autoimmune diseases, immunosuppressed patients, subjects with kidney or liver disease, HIV infection or diabetes. The Applicant provided high level clinical safety data for patients with intestinal bowel disease, HIV infected individuals, patients with kidney disease/renal failure and hepatic disease/liver transplant patients. In summary, the available clinical data in the mentioned special population subgroups did not raise concerns but are still considered limited.

While pregnant and lactating women were excluded per exclusion criteria, fourteen subjects who received at least one dose of PreHevbri reported pregnancies in the course of the study, of whom four had an AE associated with pregnancy. Three were regarded SAEs, including one spontaneous abortion, one intrauterine death of a child diagnosed with Trisomy 21 and one case of ankyloglossia congenital, with the relationship to vaccination considered unlikely. Whether PreHevbri has been administered to pregnant or lactating women during marketed use is not known.

The SmPC includes information that there are no data for use of the vaccine in pregnant woman, and that it is unknown whether the vaccine is excreted in human milk. The safety specifications includes the use in pregnancy or breastfeeding as missing information.

2.5.8.6. Immunological events

No allergic or anaphylactic reactions were reported.

2.5.8.7. Safety related to drug-drug interactions and other interactions

Specific drug-drug interactions were not assessed in the 2 pivotal trials. Specifically, administration of PreHevbri and other vaccines has not been studied, which is adequately reflected in the SmPC. The prophylactic use of antiphlogistics has not been studied, either.

An analysis of concomitantly administered medication was provided in the dossier. The submitted data did not reveal any meaningful imbalance in the 2 vaccine groups with regards to the use of concomitant medication, either in the individual studies or in the pooled analysis. The frequency of administration of concomitant medication in both vaccine groups was slightly higher in trial Sci-B-Vac-001 than in Sci-B-Vac-002, which could be explained by the different age range in these two trials. Individuals older than 45 years of age with or without well-controlled chronic disease were only included in Sci-B-Vac-001.

2.5.8.8. Discontinuation due to adverse events

In the pooled data set, 0.4% and 0.5% of subject of the Engerix-B and PreHevbri group, respectively were withdrawn from vaccination due to TEAE.

No obvious pattern in the nature of TEAE could be detected. The discontinuation of 8 subjects in the PreHevbri group were due to diagnosis of Arnold-Chiari malformation, sudden cardiac death, viral gastroenteritis, osteoarthritis, rheumatoid arthritis, dizziness, oropharyngeal pain, and migraine.

2.5.8.9. Post marketing experience

No new safety concerns arose from the post-marketing experience.

2.5.9. Discussion on clinical safety

The safety data base, including data from 2,920 subjects having been exposed to PreHevbri within the two pivotal studies, in conjunction with the data from post-marketing surveillance, with approx. 305,302 subjects having been vaccinated in a 3-dose schedule with the current formulation of the vaccine and additional data from supportive studies is considered sufficient by the CHMP.

Across both studies (pooled data) and all subgroups analysed, local reactogenicity and solicited systemic adverse events occurred more frequently in the PreHevbri group compared to Engerix-B. It

has to be taken into account, that more subjects were randomized to PreHevbri in the lot-to-lot consistency study that enrolled younger subjects, i.e. study Sci-B-Vac-002. This study reported higher frequencies for both local and system solicited reactions for both vaccines. Thus in the pooled data, younger subjects are overrepresented in the PreHevbri group.

Local AEs were reported in 55.7% and 81.4% of subjects in the Engerix-B and PreHevbri group, respectively. For the systemic solicited AEs, the differences were less pronounced, with frequencies of 54.1 % and 64.7 % also respectively. The differences in frequencies were mainly driven by higher frequency of pain and tenderness at the injection site and the solicited systemic AE of myalgia. Most of the solicited AEs (local and systemic) were mild to moderate in intensity. Frequencies of solicited local and systemic AEs were highest after the first vaccination for both vaccines.

TEAEs were reported at similar frequencies within each study and for the pooled data for both treatment arms, reported in 48.4% of subjects vaccinated with Engerix-B and 48.3% vaccinated with PreHevbri. No substantial differences were detected between the treatment groups neither with respect to the nature of the TEAE nor to its severity. Few subjects experienced an SAE, with only one being assessed as vaccine-related by the investigator (viral gastroenteritis), assessed as unrelated by the sponsor. SAEs were reported slightly more often in the PreHevbri group, driven by events in the SOC of Infections and infestations, and Injury, poisoning and procedural complications. Only few subjects were withdrawn from further dosing or from the study due to AEs.

Regarding the different subgroups analysed, higher frequencies of adverse event were generally reported in female versus male, Whites versus Black or African Americans, non-Latinos/non-Hispanics vs Latinos, non-diabetics versus diabetics, participants from Europe vs North America, except for the AE of pruritus. Of note, no allergic or anaphylactic reactions were recorded.

Regarding the lot-to-lot consistency study (Sci-B-Vac-002), similar frequencies and severity were reported for the three lots for local and systemic solicited adverse events, unsolicited, treatment emergent adverse events, TEAE leading to study withdrawal and SAEs. There was also no difference in the assessments of relatedness.

Some patient groups have been excluded from the studies, for instance patients with hepatic impairment, kidney impairment, cardiac impairment, autoimmune disease, immunocompromised patients, pregnant and lactating women. Clinical data are therefore limited. Due to scarce data in humans, PreHevbri should preferably only be used during pregnancy when there is a clear risk of hepatitis B infection and when benefit outweighs the risk. This has been adequately addressed in the SmPC.

Due to the fact, that total number of subjects in the clinical database exposed to PreHevbri was slightly below three-thousand, the lowest category of frequency for any event, even occurring in a single subjects only, was reported as “rare”. The category “very rare”, with frequencies < 1/10,000 was not applicable.

The vaccine had been licensed in several countries and post-marketing surveillance did not detect any safety signal.

Despite the fact that PreHevbri showed a higher reactogenicity profile compared to Engerix-B with respect to local reactions and, to a lesser extent, with respect to systemic solicited AEs, the safety profile is acceptable as the intensity of the solicited AEs was mostly mild to moderate and did not warrant any safety concerns. No differences between the three lots tested in study Sci-B-Vac-002 regarding safety and reactogenicity profile of the vaccine could be detected. No major differences were seen for unsolicited treatment emergent AEs or related AEs between the two vaccines.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have

been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

Overall, the submitted clinical safety data indicate an acceptable reactogenicity and safety profile for PreHevbri. No major safety concerns were identified. The safety profile of PreHevbri is considered to support a positive B/R balance.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in patients simultaneously being administered other vaccines Use in immunocompromised patients including patients with HIV infection Use in patients with autoimmune disease Use in pregnancy or breastfeeding

2.6.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
PreHevbri Pregnancy Outcomes Registry An observational, Non-interventional (Treatment Registry) surveillance program Planned	To monitor and evaluate all submitted reports of PreHevbri vaccine exposure during pregnancy, as well as maternal, obstetrical, and neonatal outcomes.	Use in pregnancy	Final protocol submission (US)	01Feb2022
			Study start date	01Mar2022
			Study completion date	31Dec2032
			Final report available	01Dec2029

2.6.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in patients simultaneously being administered other vaccines	Routine risk minimisation measures: *SmPC section 4.5 where advice is given that the concomitant use of PreHevbri with other vaccines is not recommended.* *SmPC section 6.2 where advice is given that due to the absence of compatibility studies, PreHevbri should not be mixed with other medicinal products.* *PL section 2 where advice is given to inform the doctor, pharmacist or nurse if you have recently received or might receive any other vaccine.* Legal status: Prescription only medicine. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in immunocompromised patients including patients with HIV infection	Routine risk minimisation measures: *SmPC section 4.4 where warning is given that immunocompromised persons may have a diminished immune response to PreHevbri. Attention should be given to ensure that a protective antibody level is maintained as defined by national recommendations and guidelines.* *SmPC section 4.4 where advice is given to not to preclude patients with HIV infection from vaccination against hepatitis B and physician should consider PreHevbri vaccination on a case by case basis, as hepatitis B infection can be serious in these patients.* *PL section 2 where warning is given that if patient have a weakened immune system, doctor may need to do a blood test to check if the vaccination has worked well enough to protect you against hepatitis B.* Legal status: Prescription only medicine. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cumulative regular review of post-authorisation data and submission of safety data in PSUR/PBRER. Additional pharmacovigilance activities: None
Use in patients with autoimmune disease	Routine risk minimisation measures: *PL section 2 where advice is given to inform the doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines.* Legal status: Prescription only medicine. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Cumulative regular review of post-authorisation data and submission of safety data in PSUR/PBRER. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnancy or breastfeeding	Routine risk minimisation measures: *SmPC section 4.6 where advice is given that vaccination during pregnancy should only be performed if the risk-benefit ratio at individual level outweighs possible risks for the foetus.* *SmPC section 4.6 where advice is given that a decision must be made whether to discontinue breast-feeding or to abstain from PreHevbri vaccination while taking into account the benefit of breast-feeding for the child and the benefit of vaccination for the woman, as the risk to the breastfed newborn/infant cannot be excluded.* *PL section 2 where advice is given to inform the doctor, pharmacist or nurse, if patient is pregnant or think she may be pregnant, before being given PreHevbri.* *PL section 2 where advice is given to discuss with the doctor or nurse whether the risks and benefits of breast-feeding patient's child outweigh the benefit of vaccination and whether patient should stop breast-feeding as risk to the suckling child cannot be excluded.* Legal status: Prescription only medicine. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Follow-up pregnancy form.* Additional pharmacovigilance activities: • *PreHevbri Pregnancy Outcomes* Registry

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of European Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, PreHevbri (hepatitis B surface antigen) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HBV infection causes a broad spectrum of disease severity from subclinical self-limiting infections to fulminant hepatitis or chronic infection. Up to 50% of adults develop symptomatic icteric hepatitis, which is characterized by fatigue, fever, anorexia and jaundice. Acute HBV infection can develop into a chronic disease. The likelihood that HBV infection becomes chronic is age-dependent. While infants infected with HBV in the first year of life almost universally develop chronic infection, immunocompetent adults develop chronic hepatitis at a rate of 5-10%. Immunosuppressed individuals, including those with diabetes and older adults are at an increased risk of developing chronic HBV. In adults, while acute HBV symptoms are typically transient and self-limiting, among those who become chronically infected with HBV, 20-30% will develop cirrhosis or liver cancer.

3.1.2. Available therapies and unmet medical need

Recombinant DNA-derived vaccines against HBV have been available for more than two decades. The primary hepatitis B immunization series conventionally consists of three doses of vaccine. Vaccination of infants and, in particular, delivery of hepatitis B vaccine within 24 hours of birth is 90–95% effective in preventing infection with HBV as well as decreasing HBV transmission if followed by at least two other doses. WHO recommends universal hepatitis B vaccination for all infants, and that the first dose should be given as soon as possible after birth. In the EU, the recommendations for adult HBV vaccination reflect regional differences in the hepatitis B vaccination programme, which depend on the epidemiology of HBV in the region and logistic considerations and are largely based on targeted risk-group vaccination strategies.

Adults who were not immunized as children remain at risk of becoming infected with HBV. Up to 10% of all adults fail to achieve seroprotective levels of antibodies against HBV (i.e. anti-HBs ≥10 mIU/mL) with a three-dose schedule of conventional HBV vaccines, and are considered “non-responders” to hepatitis B vaccination.

In addition to age and genetic factors, other factors are known to be associated with reduced immunogenicity of HBV vaccines in adults, including obesity, diabetes, smoking and concomitant diseases.

3.1.3. Main clinical studies

To support the authorisation of PreHevbri in Europe and North America, two Phase 3 clinical trials (Sci-B-Vac-001 and Sci-B-Vac-002) that compared PreHevbri to Engerix-B were conducted in Europe and North America to further evaluate the immunogenicity, safety and manufacturing consistency of the adult formulation to be marketed. The chosen comparator for these phase 3 trials, Engerix-B (20 µg HBsAg), is an approved standard-of-care HBV vaccine for the immunization of adults.

The phase 3 clinical development programme of PreHevbri in North America and Europe was developed with the knowledge that many people who remain at risk of HBV infection are over the age of 30 and may suffer from comorbid condition that may prevent them from mounting an effective immune response following vaccination with HBV vaccines. With this in mind, the phase 3 trial (Sci-B-Vac-001)

enrolled adults ≥18 years old, including those with well-controlled chronic diseases. Moreover, a high proportion of adults ≥45 years of age, with targeted enrolment of 40% in the 45-64 year old age group and 40% in the ≥65 year old age group, has been enrolled.

Sci-B-Vac-001 was a multicentre, double-blind, randomized, comparative, controlled study with the primary objective to establish the non-inferiority of PreHevbri compared to Engerix-B, based on the SPR 4 weeks after the third vaccination in adults (≥18 years) and the superiority of PreHevbri compared to Engerix-B in subjects ≥45 years old (co-primary objectives). Eligible subjects were men and women, 18 years of age or older, in stable health or with controlled chronic conditions. Pregnant and breastfeeding females, individuals with autoimmune disease and immunodeficiency disorders were not enrolled in the trial. Subjects were randomized in a 1:1 ratio using a web-based randomization system to receive either 3 intramuscular injections of PreHevbri or 3 injections of Engerix-B delivered at 0, 1 and 6 months and followed for 24 weeks after the third vaccination to ensure an adequate safety assessment. 1607 subjects were randomized, including 796 subjects to the PreHevbri treatment arm and 811 subjects to the Engerix-B treatment arm. All randomized subjects received their assigned treatment.

Sci-B-Vac-002 was a double-blind, 4-arm, randomized study with the primary objective to demonstrate the manufacturing equivalence of three consecutive lots of PreHevbri, in terms of immunogenicity four weeks after the third vaccination (Study Day 196). Eligible subjects were healthy men and women, 18 to 45 years of age. Pregnant and breastfeeding females, individuals with autoimmune disease and immunodeficiency disorders were not enrolled in the trial. Overall, 2838 subjects were randomized in the study, including 712 subjects in the Engerix-B group, 711 subjects in the Lot A PreHevbri group, 709 subjects in the Lot B PreHevbri group and 706 in the Lot C PreHevbri group.

The pooled safety data from the 2 pivotal phase 3 trials included a total of 2,920 individuals who received at least one dose of PreHevbri.

3.2. Favourable effects

The two co-primary analyses were (1) non inferiority of PreHevbri compared to Engerix B in subjects ≥ 18 years old at Study Day 196 and (2) superiority of PreHevbri compared to Engerix B in subjects ≥45 years old at Study Day 196. Both co-primary endpoints were met in Study Sci-B-Vac-001. These results of non-inferiority and superiority were consistent across key subgroups, which were enrolled in this study. Key subgroups were defined by age, gender, diabetes status, BMI, daily alcohol consumption and smoking habits. Women achieved higher seroprotection rates compared to male subjects in the Engerix-B and PreHevbri group. The SPR had lower values in both vaccine-arms by increasing age, smoking, BMI above 30 and more than 1 drink per day.

Exploratory analysis showed that SPR in the PreHevbri arm was more than twice as high as the SPR in the Engerix-B arm at all timepoints in the first 6 months: 16.0% vs. 7.7% at Study Day 28, 51.5% vs. 23.9% at Study Day 56, and 66.0% vs. 27.4% at Study Day 168. Furthermore, significantly higher GMCs of anti-HBs were noted for PreHevbri compared with Engerix-B at all timepoints. Markedly higher anti-HBs titers were noted after the second dose of PreHevbri (Study Day 56) with GMC of 17.25 mIU/mL as compared with 5.85 mIU/mL in the Engerix B arm. Anti-HBs titers peaked at Study Day 196 in both treatment arms with higher GMCs noted in the PreHevbri arm as compared with the Engerix-B arm (1148.31 mIU/mL vs 192.65 mIU/mL).

At all timepoints, the rate of subjects who achieved the expected anti-HBs level ≥100 mIU/mL was higher in the PreHevbri group compared to the Engerix-B group. The rate of subjects of non-responders was higher in the Engerix-B arm compared to the PreHevbri arm.

The primary immunogenicity endpoint in study Sci-B-Vac-002 of lot-to-lot consistency between the 3 batches was met for the PPS1 and FAS population. The exploratory objective to demonstrate non-inferiority of PreHevbri compared with Engerix-B was assessed by comparing the SPR induced by PreHevbri at Study Day 168 (20 weeks following the second vaccination, just prior to the third vaccination) and Engerix-B at Study Day 196 (4 weeks following the third vaccination). The statistical criterion for non-inferiority of SPR after 2 doses of PreHevbri compared with 3 doses of Engerix-B was met in the age group of adults 18-45 years. Higher mean GMC of anti-HBs were noted after vaccination with PreHevbri (pooled) compared to Engerix B after the second vaccination at Study Day 168 (118.95 mIU/mL vs 14.99 mIU/mL) and after the third vaccination at Study Day 196 (5443.07 mIU/mL vs 1526.26 mIU/mL). Similar observations regarding the rate of non-responders and subjects, who achieved the anti-HBs level ≥100 mIU/mL, were also seen in this study. The rate of non-responder was lower in subjects who received PreHevbri compared to Engerix-B.

3.3. Uncertainties and limitations about favourable effects

While the younger population in study Sci-B-Vac 002 aged 18 to 45 years who received PreHevbri achieved a SPR > 90% after two doses, PreHevbri recipients (≥ 18 years, with approximately 80% ≥ 45 years) in study Sci-B-Vac 001 required the third dose of PreHevbri to achieve these levels of seroprotection. Lower mean geometric titers at each timepoint were observed in study Sci-B-Vac 001 compared to Sci-B-Vac 002.

Immunosuppressed /immune-deficient individuals were excluded from the study. These patients may not be able to elicit a strong immune response to sufficiently protect them from infection. Data are also lacking from pregnant and breast-feeding women, as well as from individuals with unstable health conditions and comorbidities.

Interaction with other vaccines has not been evaluated during the clinical development programme of PreHevbri.

3.4. Unfavourable effects

Across both studies and all subgroups analysed, local reactogenicity and to a lesser extent solicited systemic adverse events occurred more frequently in the PreHevbri group compared to Engerix-B (PreHevbri 81.4% vs. Engerix-B 55.7%). The higher local reactogenicity was mainly driven by a higher incidence of injection site pain (72.2% and 44.5%, respectively) and tenderness (71.2% and 44.2%, respectively), which were the most commonly reported solicited local adverse reactions. Severe solicited local AEs were reported more frequently in the PreHevbri group with 2.4% of participants compared to Engerix-B with 0.9%, again driven by pain 0.7% vs 0.3% and tenderness 1.8% vs 0.5% for PreHevbri and Engerix-B, respectively. The incidence of local AEs in subjects who received PreHevbri was highest following the first vaccination (69.8%). It decreased after the second vaccination (61.3%) and remained similar after the third vaccination (61.4%). Only the incidence of pruritus was highest after the third vaccination. The difference in systemic reactogenicity was less notable in the two vaccine groups and mainly observed for myalgia (41.7% and 28.1%, respectively). The most commonly reported solicited systemic reactions beside myalgia were fatigue (37.5% versus 35.0%), and headache (36.3% versus 33.2%). Severe (Grade 3) solicited systemic reactions were reported in 2.8% and 2.6% of subjects vaccinated with PreHevbri and Engerix-B, respectively. The most common Grade 3 reaction was fatigue (PreHevbri: 1.4%, Engerix-B: 1.6%).

3.5. Uncertainties and limitations about unfavourable effects

A higher reactogenicity of PreHevbri compared to comparator vaccines has already been observed in former trials. However, concerning the higher local and systemic reactogenicity for PreHevbri in trial Sci-B-Vac 002, it has to be taken into account that the difference might be lower than the data indicate. More subjects were randomized to PreHevbri in the lot-to-lot consistency study that enrolled younger subjects who in general showed a higher reactogenicity. Thus in the pooled data, younger subjects are overrepresented in the PreHevbri group.

A total of 25 Grade 4 solicited local AEs occurred in 24 subjects (14 in PreHevbri [0.5%] and 10 in Engerix-B [0.7%] groups), comprising 20 AEs of redness and 5 AEs of swelling at injection site. These AEs were not medically-attended, and, as the subjects did not seek medical attention for the events, the presence of skin necrosis or exfoliative dermatitis could not be medically confirmed.

3.6. Effects Table

Effects Table PreHevbri, active immunisation against infection caused by all known subtypes of the hepatitis B virus in adults.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
High immune response	Higher SPR compared to Engerix-B	91.4 %	PreHevbri	Engerix-B 76,5 %		CSR Sci-B-Vac 001
	Non-responder rate lower	8,64 %	PreHevbri	Engerix-B 23,51 %		CSR Sci-B-Vac 001
High immune response	Higher GMC At Day 196	1148, 31	PreHevbri	Engerix-B 192,65 Ration of 6.05		CSR Sci-B-Vac 001
Unfavourable Effects						
Local (and to a less extent) systemic reactogenicity was higher in the PreHevbri group compared with the Engerix B vaccine group			PreHevbri	Engerix-B	The difference might be smaller than suggested by the data, due to the difference in subjects enrolled in the 2 pivotal trials with younger adults (18-45 years) enrolled in study Sci-B-Vac-002. In trial Sci-B-Vac-002, 3 times more subjects were randomized to PreHevbri than to Engerix-B.	Safety analysis set, pooled safety data from pivotal trials Sci-B-Vac-001and Sci-B-Vac-002
	Solicited local adverse events	%				

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	Any local		81.4	55.7		
	Redness/erythema		2.7	1.8		
	Pain		72.2	44.5		
	Swelling/edema		2.5	1.2		
	Tenderness		71.2	44.2		
	Pruritus/itching		12.2	10.1		
	Solicited systemic adverse events					
	Any systemic		64.7	54.1		
	Myalgia		41.7	28.1		
	Fatigue		37.5	35		
	Headache		36.3	33.2		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Though the safety data indicate a higher reactogenicity profile for PreHevbri compared to Engerix-B with respect to local reactions and to a lesser extent with respect to systemic solicited AEs, the safety profile is deemed acceptable. The intensity of solicited AEs was mostly mild to moderate. Moreover, concerning the reactogenicity for PreHevbri, the CHMP considered that the difference might be lower than the data indicate. Specifically, more subjects were randomized to PreHevbri in the lot-to-lot consistency study that enrolled younger subjects leading to an over representation of younger subjects, who in general showed a higher reactogenicity in the pooled safety data. The evaluation of unsolicited AEs and SAEs did not reveal any safety concerns. The somewhat higher reactogenicity must be weighed against the higher immune response of PreHevbri, reflected in the immunogenicity data. At all time-points, higher SPRs and GMCs were measured in the PreHevbri group compared to the Engerix-B group, even in adults aged above 45 years, were a superior immune response has been shown. The rate of non-responders was lower in the PreHevbri group compared to the Engerix-B group. Younger adults 18-45 years of age years who received PreHevbri achieved a SPR > 90% after two doses compared to recipients of 3 doses Engerix-B, which means that level of seroprotection was reached at an earlier time point. Elderly subjects required the third dose of PreHevbri to achieve these levels of seroprotection.

3.7.2. Balance of benefits and risks

The safety database comprised of pooled data from the 2 pivotal trials Study Sci-B-Vac-001 and Sci-B-Vac-002 is considered adequate. The submitted safety data did not reveal any safety concern and indicated an acceptable safety profile. Across both studies and all subgroups analysed, local reactogenicity and to a lesser extent solicited systemic adverse events occurred more frequently in the PreHevbri group compared to Engerix-B. This unfavourable reactogenicity is outweighed by a higher immune response, i.e. higher efficacy of PreHevbri as compared with Engerix-B.

Given the favourable effects concerning the immune response, a favourable B/R balance in the proposed indication is concluded. This conclusion is particularly relevant for individuals at risk of reduced immune response after hepatitis B vaccination, e.g. elderly above 65 years of age, obese individuals, and patients with diabetes mellitus etc. The superiority of PreHevbri in subjects with comorbidities was observed in the pivotal trial Sci-B-Vac 001 for the age-group 45 years and older. The advantage of PreHevbri over Engerix-B in subgroups based on intrinsic factors known to be associated with reduced immunogenicity was not evident in the age group 18-45 years (Sci-B-Vac-002).

3.7.3. Additional considerations on the benefit-risk balance

It was observed that GMC of anti-HBs titers in the PreHevbri group continued to be higher compared to the Engerix-B group up to day 336 (6 months after the third vaccination). The higher peak titers at Day 196 in the PreHevbri group in both studies were shown to translate into higher rates of seroprotection at one year (Day 336) at both the 10 mIU/mL and the 100 mIU/mL thresholds. Additionally, participants of study Sci-B-Vac-001 were recruited to take part in a study evaluating long-term persistence of anti-HBs antibodies after vaccination with 3-antigen PreHevbri vaccine, as compared to Engerix-B vaccine. 500 subjects are being invited with a ratio 1:1 to provide additional blood samples 2.5-3.0 years after having received their third study vaccination. The preliminary results of this long-term persistence study were provided by the Applicant. The 2.5 years persistence data indicated a robust and lasting immune response for PreHevbri. It was observed that the level of GMTs and seroprotection rates for the PreHevbri vaccine group were higher than for the Engerix-B-group. Moreover, the proportion of subjects in the PreHevbri group that have retained titers > 100 mIU/mL was approximately two-fold compared to the Engerix-B group.

3.8. Conclusions

The overall benefit/risk balance of PreHevbri is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of PreHevbri is favourable in the following indication(s):

> PreHevbri is indicated for active immunisation against infection caused by all known subtypes of the hepatitis B virus in adults.
>
> It can be expected that hepatitis D will also be prevented by immunisation with PreHevbri as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

The use of PreHevbri should be in accordance with official recommendations.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.