Official Protocol Title:	A Hepatitis B Vaccine Challenge Study to Demonstrate the Durability of Protection Against Hepatitis B Virus Infection in Healthy Children Vaccinated Approximately 9 Years Previously With a 2- or 3-Dose Infant Series and Toddler Dose of Vaxelis®
NCT number:	NCT04490499
Document Date:	27-Apr-2020

Title Page

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Protocol Title: A Hepatitis B Vaccine Challenge Study to Demonstrate the Durability of Protection Against Hepatitis B Virus Infection in Healthy Children Vaccinated Approximately 9 Years Previously With a 2- or 3-Dose Infant Series and Toddler Dose of Vaxelis®

Protocol Number: 013-00

Compound Number: V419

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND	Not applicable
EudraCT	2020-000126-26

Approval Date: 27 April 2020

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original Protocol	27-APR-2020	Not applicable

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Hepatitis B Vaccine Challenge Study to Demonstrate the Durability of Protection Against Hepatitis B Virus Infection in Healthy Children Vaccinated Approximately 9 Years Previously With a 2- or 3-Dose Infant Series and Toddler Dose of Vaxelis®

Short Title: A Hepatitis B Vaccine Challenge Study After Previous Vaxelis® Vaccination.

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There is no formal hypothesis testing in this study.

Primary Objectives	Primary Endpoints
- Objective: To evaluate the proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge (Day 30) with HBVAXPRO™.	- Anti-HBs level
Secondary Objectives	Secondary Endpoints
- Objective: To evaluate anti-HBs GMCs pre-challenge on Day 1 and 30 days post-challenge with HBVAXPRO™.	- Anti-HBs level

Overall Design:

Study Phase	Phase 3
Primary Purpose	Prevention
Indication	Long-term protection against HBV infection
Population	Healthy children 8 to 10 years of age who participated in Protocols V419-007 or V419-008 and received a 3 + 1 or a 2 + 1 (infant + toddler) Vaxelis® schedule, respectively
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	Not applicable
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 months from the time the first participant signs the informed consent/assent until the last participant's last study-related telephone call or visit. For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 200 participants will be enrolled in the study.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Vaccine</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Vaccination Regimen</th><th>Use</th></tr>
<tr><td>1</td><td>HBVAXPRO™</td><td>Refer to product labeling</td><td>Single dose</td><td>IM</td><td>Single dose on Day 1</td><td>Challenge Agent</td></tr>
<tr><td colspan="7">Abbreviations: admin. = administration; IM = intramuscular</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups</td><td>1 intervention group</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 1 month from the time the participant or the participant's legally acceptable representative signs the Informed Consent Form (ICF) through the final contact.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

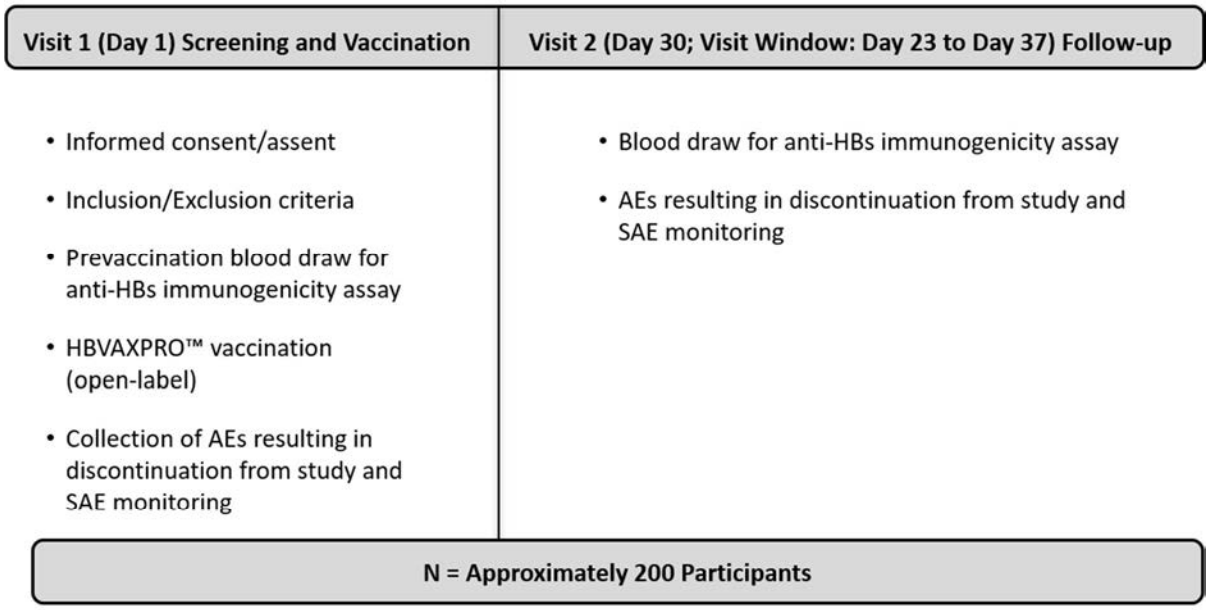
Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The key components of the study are depicted in Figure 1.

Figure 1 V419-013 Study Design



AE = adverse event
anti-HBs = hepatitis B surface antibody
SAE = serious adverse event

1.3 Schedule of Activities

Study Period:	**Intervention**		**Notes**
Visit Number:	**1**	**2**	
Scheduled Time:	**Day 1**	**Day 30**	
Visit Window:	**Not Applicable**	**Day 23 to Day 37**	
Administrative Procedures			
Screening Procedures			
Informed Consent/Assent	X		Consent/assent must be obtained before any study procedures.
Assignment of Screening Number	X		
Participant Identification Card	X		
Inclusion/Exclusion Criteria	X		Review of prior medications/vaccinations, a targeted physical examination, and temperature measurement are required at Visit 1 to determine eligibility.
Medical History	X		The participant's medical history for the 5 years prior to Visit 1 (Day 1) will be obtained.
Post-Enrollment Procedures			
Assignment of Treatment/Allocation Number	X		
Prior/Concomitant Medication and Non-Study Vaccination Review	X	X	
HBVAXPRO™ Administration (Open-label)	X		
Safety Procedures			
Targeted Physical Examination	X		To be performed by the investigator or medically qualified designee.
Body Temperature Measurement	X		Each participant's body temperature must be taken before vaccination. Participants who have febrile illness at or within 72 hours of vaccination must be rescheduled.
Postvaccination Observation Period	X		Per current local standard of care
Collection of AEs Resulting in Discontinuation and SAE Monitoring	X	X	A scripted questionnaire can be found in the Investigator Trial File Binder (or equivalent) provided by the Sponsor.
Immunogenicity Procedures			
Serum for Immunogenicity Assay	X	X	Blood samples must be collected on Day 1 before vaccination. Sera from participants will be used to measure anti-HBs concentration.

AE = adverse event; anti-HBs = hepatitis B surface antibody; SAE = serious adverse event

2 INTRODUCTION

2.1 Study Rationale

The purpose of this study is to demonstrate the durability of protection against HBV infection approximately 9 years after vaccination with Vaxelis®. Vaxelis® (diphtheria, tetanus, pertussis [acellular, component], hepatitis B [rDNA], poliomyelitis [inactivated], and Haemophilus influenzae type b conjugate vaccine [adsorbed]) (DTaP5-HB-IPV-Hib) is a hexavalent vaccine indicated for active immunization to prevent the diseases caused by these pathogens. Vaxelis® was approved in the EU in 2016 and in the US in 2018. The hepatitis B component of the vaccine contains 10 µg of HBsAg produced by recombinant DNA technology and adsorbed on aluminum.

Hepatitis B vaccination results in increases in anti-HBs. Achievement of an anti-HBs concentration ≥10 mIU/mL 1 to 2 months after completion of a primary hepatitis B vaccination series is a globally accepted serologic correlate of protection against HBV infection [Plotkin, S. A. 2010] [World Health Organization 2017]. Anti-HBs levels wane over time and 15% to 50% of children who responded to the initial series will have low or undetectable levels 5 to 15 years later [Plotkin, S. A., et al 2008]. However, long-term protection is still expected due to the immune memory response [But, D. Y-K, et al 2008] [Bialek, S. R., et al 2008] [Roznovsky, L., et al 2010] [Su, F. H., et al 2007] [van der Sande, M. A. B., et al 2007] and additional doses of hepatitis B vaccine are not required or recommended [Schillie, S., et al 2018] [Leuridan, E. 2011] [FitzSimons, David, et al 2005] [European Consensus Group on Hepatitis B Immunity 2000].

Consistent with other marketed hexavalent vaccines which include a hepatitis B component, the EMA requested a post-licensure study to assess the long-term persistence of anti-HBs 3 to 4 years after vaccination with Vaxelis® [European Medicines Agency 2013] [European Medicines Agency 2016]. The resultant study (V419-012) assessed children aged 4 to 5 years who received Vaxelis® or active comparator (Infanrix® hexa, GlaxoSmithKline Biologicals S.A, Rixensart, Belgium) in a 3 + 1 (Protocol V419-007: 3-dose primary series at 2, 3, and 4 months of age and a toddler dose at 12 months of age) or a 2 + 1 (Protocol V419-008: 2-dose primary series at 2 and 4 months of age and a toddler dose at 11 to 12 months of age) schedule. All of the children who participated in Study V419-012 had achieved an anti-HBs level of ≥10 mIU/mL after their vaccination series in V419-007 and V419-008 and were considered protected against HBV infection. The proportion of participants who had anti-HBs levels of ≥10 mIU/mL 3 to 4 years after the 3 + 1 schedule was 70.2% (95% CI: 63.1% to 76.6%) and 82.0% (95% CI: 75.8% to 87.2%) in Vaxelis® and Infanrix® hexa recipients, respectively. The proportion of participants who had anti-HBs levels of ≥10 mIU/mL 3 to 4 years after the 2+1 schedule was 65.8% (95% CI: 58.3% to 72.6%) and 83.7% (95% CI: 77.7% to 88.6%) in Vaxelis® and Infanrix® hexa recipients, respectively [CSR P012V419 2017].

Extended HBV protection after infant and toddler vaccinations has been documented with HBV-containing combination vaccines [Steiner, M., et al 2010] [Kosalaraksa, P., et al 2018] [Van Der Meeren, O., et al 2014] [Madhi, S. A., et al 2019]. Because the Phase 3 studies of

Vaxelis® (Protocols V419-007 and V419-008) were conducted approximately 9 years before the planned initiation of this protocol (V419-013), the Phase 3 cohort provides an excellent opportunity to assess long-term persistent protection against HBV infection specifically in Vaxelis® recipients.

This clinical study is designed to evaluate the long-term durability of the immune protection against HBV infection approximately 9 years after receipt of a 3 + 1 or 2 + 1 Vaxelis® series. Immune protection will be demonstrated by administering a hepatitis B vaccine (HBVAXPRO™, MSD) challenge dose. Anti-HBs levels pre- and post-challenge will be measured. A post-challenge anti-HBs level of ≥10 mIU/mL is considered evidence of persistent protection against HBV infection consistent with the other approved hexavalent vaccines in the EU [Steiner, M., et al 2010] [Kosalaraksa, P., et al 2018] [Van Der Meeren, O., et al 2014] [Madhi, S. A., et al 2019].

2.2 Background

HBV infection is caused by a DNA virus that attacks the liver and can cause both acute and chronic disease. It is estimated that approximately 257 million people worldwide are living with HBV infection [World Health Organization 2017]. The severe complications of chronic HBV infection include liver cirrhosis, liver cancer, and death. Major progress towards diminishing HBV infection has been made through the introduction of routine hepatitis B vaccination in infancy. This has been facilitated by use of hepatitis B containing multi-valent vaccines. The active component of the hepatitis B vaccine is the viral surface protein (HBsAg). Response to this protein (anti-HBs) is an indicator of response to the vaccine. An anti-HBs level of ≥10 mIU/mL measured 1 to 2 months after administration of the last dose of the primary vaccination series is considered a reliable serological marker of protection against HBV infection [Plotkin, S. A. 2010] [World Health Organization 2017].

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety, efficacy, and immunogenicity (as applicable) of a medicine or vaccine.

HBVAXPRO™ has a well-defined safety profile. The benefit of a hepatitis B vaccine challenge dose has not been established. Additional doses of hepatitis B vaccine are often given to persons who are perceived to be at increased risk for exposure to the virus (for example health care workers or patients on dialysis) [Hess, L., et al 2020]. Review of post-marketing safety reports on patients who received 3 or more doses of hepatitis B vaccine [recombinant] did not identify any safety concerns.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the informed consent/assent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There is no formal hypothesis testing in this study.

Objectives	Endpoints
Primary	
• **Objective**: To evaluate the proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge (Day 30) with HBVAXPRO™.	• Anti-HBs level
Secondary	
• **Objective**: To evaluate anti-HBs GMCs pre-challenge on Day 1 and 30 days post-challenge with HBVAXPRO™.	• Anti-HBs level

4 STUDY DESIGN

4.1 Overall Design

This is a single group, open-label, single-dose, and multi-site study conducted in Finland in healthy participants 8 to 10 years of age who participated in Protocols V419-007 or V419-008 and received a 3 + 1 or a 2 + 1 (infant + toddler) Vaxelis® schedule, respectively. Study participants are challenged with HBVAXPRO™ vaccine in this study.

Blood samples for immunogenicity assays will be drawn immediately before vaccination at Visit 1 (Day 1) and at 30 days post-challenge at Visit 2 (Day 30).

Information for SAEs, regardless of whether the events are considered vaccine-related by the investigator, will be collected from the time consent is signed through completion of participation in the study. AEs resulting in discontinuation from study will also be collected. This information will be collected using the scripted questionnaire found in the Investigator Trial File Binder (or equivalent) provided by the Sponsor.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The purpose of this study is to demonstrate durable protection against HBV infection approximately 9 years after vaccination with Vaxelis®. This will be done by using a hepatitis B "challenge" in the form of a HBV vaccine (HBVAXPRO™). Antibody responses to hepatitis B vaccination wane over time and continued protection against HBV infection is expected through immune memory. Long-term protection against HBV infection, which is indicative of immune memory from prior vaccination, can be demonstrated in different ways. It is most commonly demonstrated by measuring anti-HBs levels before and after a challenge dose of HBV surface antigen, ie, a HBV vaccine [Leuridan, E. 2011] [Brunskole Hummel, I., et al 2016] [Van Damme, P., et al 2019].

The risks for acquiring HBV infection vary throughout life. It is highest in infancy and during the first 5 years of life and then is affected later in life by behavioral factors and health status. The timing of the prior Vaxelis® Phase 3 studies (V419-007 and V419-008) and the age of the participants, which is prior to onset of increased risk activities, make this an excellent opportunity to evaluate ongoing protection by demonstrating responses before and after a HBV vaccine challenge. This has been demonstrated for other hepatitis B-containing multi-valent vaccines through similar HBV vaccine challenge studies [Steiner, M., et al 2010] [Kosalaraksa, P., et al 2018] [Van Der Meeren, O., et al 2014].

This study design facilitates the demonstration of the persistence of the protective immune response against HBV infection using a hepatitis B vaccine challenge. Measurement and evaluation of pre- and post-challenge anti-HBs levels will enable demonstration of protective immunity against HBV.

Rapid increases in antibody levels within a short period after antigen challenge (ie, an anamnestic response) are an indication of the presence of immune memory. HBV infection, however, has a long incubation period (from 30 to 180 days with an average of 75 days) and the anamnestic response may take longer to peak [World Health Organization 2017]. Studies assessing early responses at 7 or 14 days post-challenge have shown response rates of 20% or 50% respectively, but reaching up to 100% by 30 days [FitzSimons, David, et al 2005] [Sharma, R., et al 2015] [Leuridan, E. 2011] [Van Damme, P., et al 2019] [Hammitt, L. L., et al 2007] [Jan, C. F., et al 2010]. In order to capture full response to the challenge dose, this study will measure anti-HBs responses at 30 days post-challenge. Given the long incubation period of the HBV infection, an immune response measured at 30 days post-challenge (ie, exposure) is an adequate time point to measure early enough response to protect against infection.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

The primary immunogenicity endpoint for the study is the proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge with HBVAXPRO™. The anti-HBs concentration of ≥10 mIU/mL is a serologic correlate of protection that is widely accepted as the threshold for protection against HBV infection [Plotkin, S. A. 2010]

[World Health Organization 2017]. Attaining the ≥10 mIU/mL threshold after a single challenge dose of HBV vaccine (in the setting of completion of a prior hepatitis B vaccination series) is a commonly used and accepted method to demonstrate the persistence of protection against HBV infection [Schillie, S., et al 2018]. Response to a single primary dose of HBV vaccine in an individual who is vaccine-naïve, is generally not sufficient to achieve this protective concentration. It is for this reason that a 2- or 3- dose primary series is required for protection in HBV vaccine-naïve individuals [Cassidy, W. M., et al 2001] [Schillie, S., et al 2018]. Furthermore, the response to a challenge dose (ie, after a prior vaccination series) can be differentiated from that of a response to a single vaccine in a HBV vaccine-naïve participant, by the significantly higher GMC achieved in the setting of a challenge and a higher proportion achieving anti-HBs ≥10 mIU/mL [Cassidy, W. M., et al 2001] [Hammitt, L. L., et al 2007].

4.3 Justification for Dose

HBVAXPRO™ is a well-established hepatitis B vaccine that has been used worldwide since its initial licensure in 1986. The dose of 5 µg (0.5 mL) is approved for persons from birth through 15 years of age.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent/assent form. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

1. Is healthy (based on a review of medical history and targeted physical examination) based on the clinical judgment of the investigator.

2. Has participated in Protocol V419-007 and received a 3 + 1 Vaxelis® schedule or participated in Protocol V419-008 and received a 2 + 1 Vaxelis® schedule.

Demographics

3. Is male or female, 8 years to 10 years of age, at the time of signing the informed consent/assent.

Informed Consent/Assent

4. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has a history of diagnosis (clinical, serological, or microbiological) of HBV infection.

2. Has a known or suspected impairment of immunological function (eg, HIV, splenectomy).

3. Has a known hypersensitivity to any component of the study vaccine.

4. Has a known or suspected blood dyscrasias, leukemia, lymphomas of any type or other malignant neoplasms affecting the haematopoietic and lymphatic system.

5. Has a bleeding disorder contraindicating intramuscular vaccinations.

6. *Had a recent febrile illness (defined as oral temperature ≥38.1°C [≥100.5°F]; axillary temperature ≥37.8°C [≥100.0°F]) occurring within 72 hours prior to receipt of study vaccine.

Prior/Concomitant Therapy

7. Has received any hepatitis B vaccine after participation in Protocol V419-007 or V419-008.

8. *Is receiving immunosuppressive therapy, including chemotherapeutic agents used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease.

9. *Meets one or more of the following systemic steroid exclusion criteria:

    a. Has received any dose of systemic steroids within 7 days prior to entering study.

    b. Is expected to require systemic steroids ≥20 mg/day for ≥5 consecutive days through the course of the participant's participation in the study.

    Note: Topical, ophthalmic, intra-articular or soft-tissue (eg, bursa, tendon steroid injections), and inhaled/nebulized steroids are permitted.

10. *Has received any licensed, non-live vaccine within the 14 days before receipt of study vaccine or is scheduled to receive any licensed, non-live vaccine within 30 days following receipt of any study vaccine. **Exception**: Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of any study vaccine or at least 15 days after receipt of any study vaccine.

11. *Has received any licensed live vaccine within 30 days before receipt of study vaccine or is scheduled to receive any live vaccine within 30 days following receipt of any study vaccine.

12. *Has received a blood transfusion or blood products, including immunoglobulins within the 6 months before receipt of study vaccine or is scheduled to receive a blood transfusion or blood product within 30 days of receipt of study vaccine. Autologous blood transfusions are not considered an exclusion criterion.

Prior/Concurrent Clinical Study Experience

13. *Has participated in another clinical study of an investigational product within 2 months before study vaccination at Visit 1 (Day 1) or plans to participate anytime during the duration of the current clinical study. Participants enrolled in observational studies may be included; these will be reviewed on a case-by-case basis for approval by the Sponsor.

Diagnostic Assessments

Not applicable

Other Exclusions

14 Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

For items with an asterisk (*), if the participant meets these exclusion criteria, the Day 1 Visit may be rescheduled for a time when these criteria are not met.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study, but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (HBVAXPRO™) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 1.

Table 1 Study Intervention

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Admin.	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
1	Experimental	HBVAXPRO™	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to Product labeling	0.5 mL	IM	Single dose on Day 1	Challenge Agent	NIMP	Central

admin. = administration; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided inSection 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the vaccine administered.

6.4 Study Intervention Compliance

Participants will receive single-dose of HBVAXPRO™ administered at the study site. The date and time of administration will be recorded in the source document and in the eCRF.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (see Section 5.2 for details). Systemic steroids ≥20 mg/day for ≥5 consecutive days are prohibited through the course of the study.

If there is a clinical indication for any medications or vaccinations specifically prohibited, the investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant in the study requires the mutual agreement of the investigator, the Sponsor, and the participant or the participant's legally acceptable representative.

If a medical condition requires the use of a prohibited steroid regimen, immunoglobulin, blood, or blood products during a participant's participation in this study, one of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible. Any concurrent medication or medical treatment must be recorded on the appropriate eCRF.

No other investigational compound or device may be administered at any time during this study without prior approval by the Sponsor.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

No dose modification is allowed in this study.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur prior to the intervention and generally represents withdrawal from the study.

Participants who receive a single-dose intervention cannot discontinue study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 7 mL (3.5 mL at each of Visits 1 and 2).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent/assent is in place.

8.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the participant before participation in the study.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements. The assent, as applicable, will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study. The investigator should consult with the Sponsor's Clinical Director for any questions about participant eligibility.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent/assent. At the time of intervention allocation, site personnel will add the treatment/allocation number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

The participant's medical history for the 5 years prior to Visit 1 (Day 1) will be obtained by the investigator or qualified designee at Visit 1 (Day 1) before vaccination.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The collection of previous medications and vaccinations (within the 30 days prior to Visit 1/Day 1) will be limited to the not allowed medications and vaccinations that should have led to the participant's ineligibility (see Section 5.2); these medications and vaccinations, if any, should be recorded in the eCRF.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication and non-study vaccination on the appropriate eCRF, if any, taken by the participant during the study per data entry guidelines.

If a medical condition requires the use of a prohibited steroid regimen, immunoglobulin, blood, or blood products during a participant's participation in this study, one of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.12.1.

8.1.7 Assignment of Treatment/Allocation Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/allocation number. The treatment/allocation number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/allocation number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/allocation number.

8.1.8 Study Intervention Administration

Study vaccines should be prepared and administered by appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance.

Study intervention is given on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

8.1.8.1 Timing of Dose Administration

Study vaccine will be administered as indicated in Section 1.3. All participants will be monitored for any immediate reactions as per local standard of care.

Participants must be afebrile for at least 72 hours prior to vaccination (Section 1.3).

Blood samples must be collected before study vaccination on Day 1.

8.1.9 Discontinuation and Withdrawal

Participants who receive a single-dose intervention cannot discontinue study intervention (see Section 7.1).

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit (Visit 2) at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Immunogenicity Assessments

Sera from participants will be used to measure anti-HBs concentration using the hepatitis B ECi assay.

Blood collection, storage and shipment instructions for serum samples will be provided in the operations/laboratory manual.

8.2.1 Hepatitis B ECi Assay

The purpose of the hepatitis B ECi assay is to detect total antibody to human plasma-derived HBsAg subtypes ad and ay before and after vaccination with HBsAg containing vaccine(s). This is the primary assay used to evaluate the serological response to the vaccine(s). The assay is a solid phase sandwich enzyme-labeled immunoassay. Results for the assay are reported in mIU/mL.

This assay involves the reaction of anti-HBs in a test sample with HBsAg (ad and ay subtypes) coated onto the wells. An HRP-labeled HBsAg conjugate (ad and ay subtypes) then formed a complex with the bound anti-HBs, forming an “antigen sandwich”. Unbound materials were removed by washing. A reagent that contained luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent was added to the wells. The HRP in the bound conjugate catalyzed the oxidation of the luminol derivative, producing light. The electron transfer agent increased the level and duration of the light produced. The amount of HRP conjugate bound and subsequent light produced was indicative of the concentration of anti-HBs present in the sample.

Three internally prepared control serum pools, consisting of a high-positive, low-positive, and negative control, were used to monitor the performance of the assay. These pools were each prepared from 4 individual human immune sera obtained from an external vendor. Additionally, there were anti-HBs positive and negative manufacturer-supplied controls, which were prepared from freeze-dried recalcified human plasma. The hepatitis B WHO International reference standard at 10 mIU/mL was also run as a control in every assay. The LLOQ of the assay is 5 mIU/mL.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided in this section.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A targeted physical examination will be performed as indicated in Section 1.3. Any clinically significant abnormality will be recorded on the appropriate eCRF. The targeted physical examination procedure includes obtaining vital signs (heart rate, respiratory rate, and body temperature), auscultation of the heart and lung, and examination of the abdomen, further assessment if deemed necessary by the investigator or medically qualified designee.

Findings related to the physical examinations should be documented in the participant's chart/source documentation.

8.3.2 Body Temperature Measurement

Pre-vaccination body temperature will be taken by study staff as indicated in Section 1.3. Participants who have febrile illness (defined as oral temperature ≥38.1°C [≥100.5°F] or axillary ≥37.8°C [≥100.0°F]) within 72 hours of vaccination must be rescheduled.

Oral is the preferred method of obtaining participant's temperature. If an axillary temperature is reported to be ≥37.8°C (≥100.0°F), an oral temperature must be taken. Temperature readings should be taken at approximately the same time each day. Use of temporal or tympanic thermometers to collect temperature for this study is prohibited.

8.3.3 Clinical Laboratory Assessments

There are no laboratory safety evaluations required by the protocol.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of a NSAE that leads to exclusion from study or results in discontinuation from study or SAE as well as other reportable safety events. Investigators remain responsible for following up NSAEs that lead to exclusion from study or result in discontinuation from study, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of a NSAE that leads to exclusion from study or results in discontinuation from study or SAE as well as other reportable safety events with respect to seriousness, intensity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before allocation must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

NSAEs that lead to exclusion from study or result in discontinuation from study, SAEs including death, and other reportable safety events must be reported by the investigator throughout the duration of the individual's participation in the study, regardless of whether or not related to the Sponsor's product.

Investigators are not obligated to actively seek NSAEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up NSAEs that lead to exclusion from study or result in discontinuation from study, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated Table 2.

Table 2 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report if: - led to discontinuation from study	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. - any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	There are no events of clinical interest for this study.			
ECI (do not require regulatory reporting)	There are no events of clinical interest for this study.			
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting NSAEs that lead to exclusion from study or result in discontinuation from study and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial NSAE that lead to exclusion from study or result in discontinuation from study /SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all NSAEs that lead to exclusion from study or result in discontinuation from study that occur in

allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.4.7 Events of Clinical Interest

8.5 Treatment of Overdose

In this study, an overdose is the administration of more than 1 dose of study vaccine.

No specific information is available on the treatment of overdose.

All reports of overdose must be reported by the investigator within 5 calendar days to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in

the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.10 Future Biomedical Research Sample Collection

Not applicable

8.11 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Screening procedures/eligibility criteria will be conducted at Visit 1 as outlined in Section 1.3. Screening procedures may be repeated after consultation with the Sponsor.

8.12.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized will be documented in an sSAP and referenced in the CSR for the study. Post-hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Hepatitis B Vaccine Challenge Study to Demonstrate the Durability of Protection Against Hepatitis B Virus Infection in Healthy Children Vaccinated Approximately 9 Years Previously With a 2- or 3-Dose Infant Series and Toddler Dose of Vaxelis®
Treatment Assignment	This is a single group, open-label, non-randomized study. Participants will receive a single-dose of HBVAXPRO™.
Analysis Populations	Immunogenicity: Per-Protocol (PP); Safety: All Participants as Treated (APaT)
Primary Endpoint	Immunogenicity: proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge with HBVAXPRO™
Key Secondary Endpoint	Immunogenicity: anti-HBs GMCs pre-challenge on Day 1 and 30 days post-challenge with HBVAXPRO™
Statistical Methods for Key Immunogenicity Analyses	No statistical hypothesis testing will be performed for immunogenicity analyses in this study. For the immunogenicity endpoint, the point estimates and corresponding 95% CIs will be provided.
Statistical Methods for Key Safety Analyses	Any AEs resulting in discontinuation from study and SAEs will be reported and summarized descriptively.
Interim Analyses	No interim analyses are planned for this study.
Multiplicity	No statistical hypothesis testing will be performed for immunogenicity analyses in this study. Therefore, no adjustments for multiplicity are needed in this study.
Sample Size and Power	This is an estimation study. This study will enroll approximately 200 participants and will allow estimation of the primary immunogenicity endpoint with a 95% CI.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as a non-randomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant vaccination assignments after each participant is enrolled and vaccination is assigned.

The Clinical Biostatistics department will generate the allocation schedule(s) for study treatment assignment.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3. This is an estimation study, and no formal hypothesis testing will be performed.

9.4 Analysis Endpoints

Immunogenicity and safety endpoints that will be evaluated are listed below.

9.4.1 Immunogenicity Endpoints

The primary immunogenicity endpoint is the proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge with HBVAXPRO™, described in Section 3 and Section 4.2.1.1.

The secondary immunogenicity endpoint is the anti-HBs GMCs pre-challenge on Day 1 and 30 days post-challenge with HBVAXPRO™.

The exploratory immunogenicity endpoint includes the proportion of participants with a ≥4-fold rise in anti-HBs level from pre-challenge on Day 1 to 30 days post-challenge with HBVAXPRO™.

9.4.2 Safety Endpoints

This study will monitor safety through the collection of AEs resulting in discontinuation from study and SAEs at Visit 1 and Visit 2 (Day 30).

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of immunogenicity data in this study. The PP population consists of all enrolled participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint. Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive study vaccine at Visit 1 (Day 1)
- Receipt of a prohibited medication or prohibited vaccine prior to study vaccination
- Receipt of a prohibited medication or prohibited vaccine prior to blood sample collection at Visit 2 (Day 30)
- Collection of a blood sample at Visit 2 outside of the pre-specified analysis window (Day 23 to Day 44)

9.5.2 Safety Analysis Populations

Safety summaries will be conducted in the APaT population, which consists of all participants who received study vaccine and had safety follow-up data after the vaccination.

9.6 Statistical Methods

Statistical methods relating to immunogenicity analyses are described in Section 9.6.1. Statistical methods relating to safety analyses are described in Section 9.6.2.

9.6.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the immunogenicity objectives. No statistical hypothesis testing will be performed for immunogenicity analyses in this study. Point estimates and 95% CIs will be provided for both the primary and secondary immunogenicity objectives.

The point estimate for the primary immunogenicity objective will be calculated as the proportion of participants with a protective anti-HBs level of ≥10 mIU/mL at 30 days post-challenge with HBVAXPRO™. The CIs will be calculated based on the exact method proposed by Clopper and Pearson [Collett, D. 1999].

The point estimates for the secondary immunogenicity objective will be calculated by exponentiating the estimates of the mean of the natural log values. The 95% CIs will be derived by exponentiating the bounds of the CIs of the mean of the natural log values based on the t-distribution.

9.6.2 Statistical Methods for Safety Analyses

The proportion of participants with AEs resulting in discontinuation from study and any SAEs will be reported and summarized descriptively. The point estimates and the 95% CIs will be calculated using the Clopper Pearson method [Collett, D. 1999].

9.7 Interim Analyses

No interim analyses are planned for this study.

9.8 Multiplicity

No statistical hypothesis testing will be performed for immunogenicity analyses in this study. Therefore, no multiplicity adjustment is required in this study.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

Since this is an estimation study, no formal power calculation for immunogenicity was performed. This study will enroll approximately 200 participants and will allow estimation of the primary immunogenicity endpoint with a 95% CI with a half-width of 4.0 percentage points. This is based on the following assumptions: 1) approximately 200 participants enrolled, 2) an underlying response rate of 95%. The calculation is based on the exact binomial method proposed by Clopper and Pearson [Collett, D. 1999]. In order to evaluate the potential impact of limited enrollment and attenuated response rate, the half-width of the 95% CI is evaluated under different sample size and response rate assumptions. Table 3 summarizes estimates of the half-width of the CI under various sample size and response rate.

Table 3 Estimates of the Half-width of the 95% Confidence Interval Under Different Assumptions

Evaluable Sample Size	Assumed Response Rate		
	85%	90%	95%
125	7.5%	6.6%	5.4%
150	6.7%	6.0%	4.7%
175	6.1%	5.4%	4.4%
200	5.7%	5.0%	4.0%
225	5.4%	4.7%	3.7%

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying percentage of participants with an SAE in the study population. If the underlying incidence of an SAE is 0.80% (1 of every 124 participants receiving the vaccine), there is an 80% chance of observing at least 1 SAE among 200 participants. If the underlying incidence of an SAE is 0.35% (1 of every 289 participants receiving the vaccine), there is an 50% chance of observing at least 1 SAE among 200 participants. If no SAEs are observed among the 200 participants, this study will provide 95% confidence that the underlying percentage of participants with SAE is <1.49% (one in every 67 participants).

9.10 Subgroup Analyses

For both primary and secondary immunogenicity endpoints, the point estimates will be calculated by subgroup of prior Vaxelis® schedule, respectively (ie, 3 + 1 schedule in Protocol V419-007, 2 + 1 schedule in Protocol V419-008). The point estimates and corresponding 95% CIs will be reported for each subgroup.

9.11 Compliance (Medication Adherence)

Given that participants will receive just a single dose of HBVAXPRO™, compliance will not be calculated.

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of subjects vaccinated with HBVAXPRO™.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations, (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

Not applicable

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

There are no laboratory safety evaluations required by the protocol.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

  Note: Congenital disorders (eg, present from birth) not detected or diagnosed prior to study intervention administration do not qualify for reporting as AE.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

· For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE that leads to exclusion from study or results in discontinuation from study and SAE recording

- When a NSAE leads to exclusion from study or results in discontinuation from study/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant NSAE that leads to exclusion or results in discontinuation from study /SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the NSAE that lead to exclusion or results in discontinuation from study/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each NSAE that led to exclusion from study or resulted in discontinuation from study and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies definitely acting like something is wrong).

    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the NSAE resulting in discontinuation from study or SAE?

- The determination of the likelihood that the Sponsor's product caused the NSAE resulting in discontinuation from study or SAE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference

guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the NSAE resulting in discontinuation from study or SAE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the NSAE resulting in discontinuation from study or SAE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the NSAE resulting in discontinuation from study or SAE:

    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?

    - **Time Course:** Did the NSAE resulting in discontinuation from study or SAE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the NSAE resulting in discontinuation from study or SAE compatible with a vaccine-induced effect?

    - **Likely Cause:** Is the NSAE resulting in discontinuation from study or SAE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

    - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in the study?

        - If yes, did the NSAE resulting in discontinuation from study or SAE recur or worsen?

        - If yes, this is a positive rechallenge.

        - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial NSAE resulting in discontinuation from study or SAE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the NSAE resulting in discontinuation from study or SAE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

    - Yes, there is a reasonable possibility of Sponsor's product relationship:

        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the NSAE resulting in discontinuation from study or SAE onset relative to the administration of the Sponsor's product is reasonable. The NSAE resulting in discontinuation from study or SAE is more likely explained by the Sponsor's product than by another cause.

    - No, there is not a reasonable possibility of Sponsor's product relationship:

        - Participant did not receive the Sponsor's product OR temporal sequence of the NSAE resulting in discontinuation from study or SAE onset relative to administration of the Sponsor's product is not reasonable OR the NSAE resulting in discontinuation from study or SAE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated NSAE resulting in discontinuation from study or SAE.)

- For each NSAE resulting in discontinuation from study /SAE, the investigator must document in the medical notes that he/she has reviewed the NSAE resulting in discontinuation from study /SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of NSAE Resulting in Discontinuation From Study and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the NSAE resulted in discontinuation from study or SAE as fully as possible. This may include additional laboratory tests or

investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

NSAEs that led to exclusion from study or result in discontinuation from study, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

HBVAXPRO™ has a well-defined safety profile. There is no contraindication in pregnancy.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable

10.7 Appendix 7: Country-specific Requirements

Not applicable

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
anti-HBs	hepatitis B surface antibody
APaT	All Participants as Treated
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
ECi	enhanced chemiluminescence
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
EU	European Union
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMC	geometric mean concentration
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HRP	horseradish peroxidase
HRT	hormone replacement therapy
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLOQ	lower limit of quantification
NSAE	nonserious adverse event
PK	pharmacokinetic
PP	per-protocol
SAE	serious adverse event
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
US	United States
WHO	World Health Organization
WOCBP	women of childbearing potential

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