Official Protocol Title:	A Phase 4, Open-label, Multicenter Study to Evaluate the Safety, Tolerability, and Immunogenicity of Vaxelis™ in Healthy Children Previously Vaccinated With a 2-Dose Primary Infant Series of Either Vaxelis™ or Hexyon™
NCT number:	NCT05289271
Document Date:	08-Jul-2022

Title Page

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Protocol Title: A Phase 4, Open-label, Multicenter Study to Evaluate the Safety, Tolerability, and Immunogenicity of Vaxelis™ in Healthy Children Previously Vaccinated With a 2-Dose Primary Infant Series of Either Vaxelis™ or Hexyon™

Protocol Number: 016-01

Compound Number: V419

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	Not applicable
EudraCT	2021-004053-23

Approval Date: 08 July 2022

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
Amendment 01	08-JUL-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Original Protocol	05-NOV-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 4, Open-label, Multicenter Study to Evaluate the Safety, Tolerability, and Immunogenicity of Vaxelis™ in Healthy Children Previously Vaccinated With a 2-Dose Primary Infant Series of Either Vaxelis™ or Hexyon™

Short Title: Safety, Tolerability, and Immunogenicity of Vaxelis™ after an Infant Series of either Vaxelis™ or Hexyon™

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

There is no hypothesis testing in this study.

The following objectives and endpoints will be evaluated in healthy participants who were previously vaccinated with a 2-dose primary infant series of either Vaxelis™ or Hexyon™ and who will receive a booster dose of Vaxelis™ at approximately 11 to 13 months of age.

Objectives	Endpoints
Primary	
• Objective: To evaluate the safety and tolerability of a booster dose of Vaxelis™ with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs from Day 1 through Day 5 postvaccination • Solicited systemic AEs from Day 1 through Day 5 postvaccination • Unsolicited AEs from Day 1 through Day 15 postvaccination • Serious adverse events (SAEs) through completion of study participation
• Objective: To describe the response rates to antigens contained in both Vaxelis™ and Hexyon™ 30 days after a booster dose of Vaxelis™.	Antibody responses to: • diphtheria toxoid • tetanus toxoid • pertussis toxoid (PT) • filamentous hemagglutinin (FHA) • *Haemophilus influenzae* type b polyribosylribitol phosphate (Hib-PRP) • hepatitis B surface antigen (HBsAg) • poliovirus serotypes 1, 2, and 3 at 30 days postvaccination with Vaxelis™

Objectives	Endpoints
Secondary	
• Objective: To describe the response rates to the pertussis antigens contained in Vaxelis™, but not in Hexyon™, 30 days after a booster dose of Vaxelis™.	Antibody responses to: • pertactin (PRN) • fimbriae 2/3 (FIM 2/3) at 30 days postvaccination with Vaxelis™

Overall Design:

Study Phase	Phase 4
Primary Purpose	Prevention
Indication	Vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive diseases caused by *Haemophilus influenzae* type b
Population	Healthy participants approximately 11 to 13 months of age previously vaccinated with a 2-dose primary infant series of either Vaxelis™ or Hexyon™ at 2 and 4 months of age
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	No treatment control
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 (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. 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 160 participants will be enrolled, with approximately 80 participants in each group.

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>Group 1: V,V,V[a]</td><td rowspan="2">Vaxelis™</td><td rowspan="2">Refer to product labeling</td><td rowspan="2">Single dose</td><td rowspan="2">IM</td><td rowspan="2">Single dose on Day 1</td><td rowspan="2">Experimental</td></tr>
<tr><td>Group 2: H,H,V[b]</td></tr>
<tr><td colspan="7">admin.=administration; IM=intramuscular; V=Vaxelis™; H=Hexyon™
a Participants had previously received 2 doses of Vaxelis™ at approximately 2 and 4 months of age.
b Participants had previously received 2 doses of Hexyon™ at approximately 2 and 4 months of age.</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2 intervention groups</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 30 days from the time the participant’s legally acceptable representative provides documented informed consent through the final contact.</td></tr>
</table>

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
There are no governance committees in this study.	

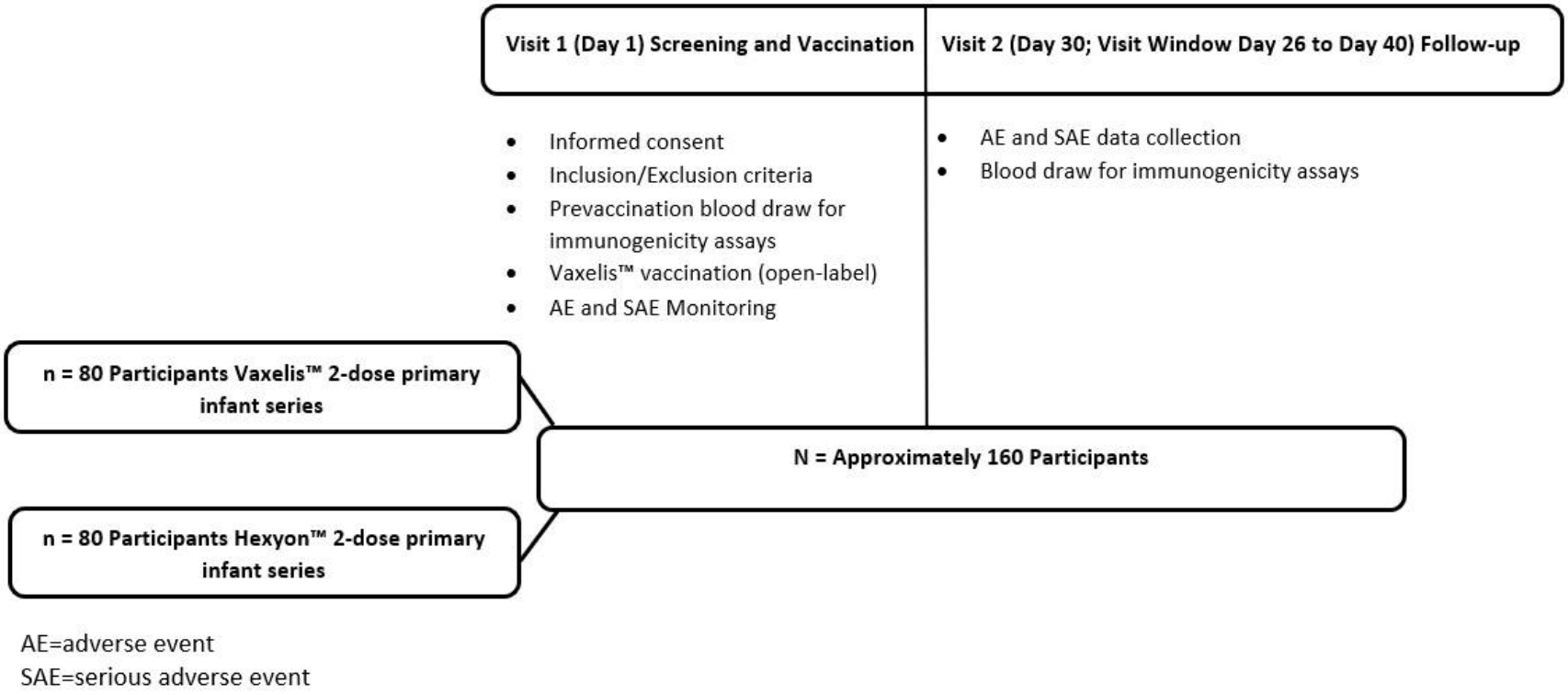
Study Accepts Healthy Volunteers: Yes

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

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 V419-016 Study Design



AE=adverse event
SAE=serious adverse event

1.3 Schedule of Activities

Study Period	**Intervention**		**Notes**
Visit Number	**1**	**2**	
Scheduled Day	**Day 1**	**Day 30**	
Visit Window	**NA**	**Days 26 to 40**	
Administrative Procedures			
Screening Procedures			
Informed Consent	X		Consent must be obtained before any study procedures.
Assignment of Screening Number	X		
Inclusion/Exclusion Criteria	X		Review of prior medications/vaccinations, a physical examination, and temperature measurement are required at Visit 1 to determine eligibility.
Participant Identification Card	X		
Medical History	X		See Section 8.1.4 for details.
Post-Enrollment Procedures			
Assignment of Allocation Number	X		
Prior/Concomitant Medication and Nonstudy Vaccination Review	X	X	See Section 8.1.5 for details. Nonstudy, non-live pediatric vaccines are permitted to be administered in a separate limb and after study vaccination on Day 1. Nonstudy, live and non-live pediatric vaccines are permitted after blood draw on Day 30.
Vaxelis™ Administration (Open-label)	X		
Safety Procedures			
Full Physical Examination	X		To be performed by the investigator or medically qualified designee before study vaccine is administered.
Body Temperature Measurement	X		Each participant's body temperature must be taken before vaccination. Participants who have febrile illness (defined as rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) at or within 72 hours of vaccination must be rescheduled.
Provide VRC	X		A paper VRC will be provided at Visit 1 to record AEs, body temperature, concomitant medications, and nonstudy vaccinations (see Section 8.3.3 for details). Instructions for using the VRC will be reviewed with the participant's legally acceptable representative.
AE/SAE Monitoring	X	X	See Section 8.4 for details.
Collection of VRC Information		X	
15-Minute Postvaccination Observation Period	X		The observation period can be extended if clinically indicated.

Study Period	**Intervention**		**Notes**
Visit Number	**1**	**2**	
Scheduled Day	**Day 1**	**Day 30**	
Visit Window	**NA**	**Days 26 to 40**	
Immunogenicity Procedures			
Serum for Immunogenicity Assay	X	X	Blood samples at Visit 1 and Visit 2 must be collected before any vaccination (including study vaccine and nonstudy vaccines).
AE=adverse event; NA=not applicable; SAE=serious adverse event; VRC=Vaccination Report Card			

2 INTRODUCTION

2.1 Study Rationale

Vaxelis™ (DTaP-HB-IPV-Hib) is a hexavalent combination vaccine indicated for primary and booster vaccination in infants and toddlers for the prevention of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive disease caused by *Haemophilus influenzae* type b. It can be used as a 2- or 3-dose primary series beginning at 6 weeks of age, followed by a booster dose, given at least 6 months after the primary series.

This is an open-label study of Vaxelis™ in healthy participants approximately 11 to 13 months of age who previously received a 2-dose primary infant series of either Vaxelis™ (Group 1: V,V,V) or Hexyon™ (Group 2: H,H,V) at 2 and 4 months of age as part of their routine vaccination. A 0.5-mL intramuscular dose of Vaxelis™ (open-label) will be administered to all study participants at Visit 1 (Day 1).

In clinical practice, switching between childhood hexavalent vaccines is sometimes necessary, which results in a “mixed” vaccine schedule. This may occur due to changes in vaccine availability, changes in procurement, vaccine shortages, relocation, or care provider preference. Interchangeability studies assessing this “mixed” schedule have been conducted with Hexyon™ where Hexyon™ was used as a booster in individuals who had previously been vaccinated with another hexavalent vaccine (INFANRIX™ hexa) [Aquino, A. G. B., et al 2012] [Lopez, P., et al 2017]. There are no clinical study data describing the safety and immunogenicity of Vaxelis™ used as a booster dose when another hexavalent combination vaccine was given for the primary infant series.

The purpose of this study is to describe the safety, tolerability, and immunogenicity of a booster dose of Vaxelis™ administered to healthy participants approximately 11 to 13 months of age who previously received a 2-dose primary infant series of either Vaxelis™ (Group 1) or Hexyon™ (Group 2) as part of their routine vaccinations. The immune response to this booster dose of Vaxelis™ will be evaluated for each antigen contained in both vaccines for all participants (Group 1 and Group 2) (Table 1). The immune responses to PRN and FIM 2/3 in children who received Hexyon™ during infancy and a booster dose of Vaxelis™ during the study (Group 2), will also be described.

Table 1 Vaccine Composition

One dose (0.5 mL) contains the following antigens:			
Vaxelis™		**Hexyon™**	
Antigen	**Amount in Vaxelis™**	**Antigen**	**Amount in Hexyon™**
Diphtheria toxoid	Not less than 20 IU	Diphtheria toxoid	Not less than 20 IU
Tetanus toxoid	Not less than 40 IU	Tetanus toxoid	Not less than 40 IU
Bordetella pertussis antigens Pertussis toxoid (PT) Filamentous haemagglutinin (FHA) Pertactin (PRN)[a] Fimbriae Types 2[a] and 3[a] (FIM2/3)	 20 micrograms 20 micrograms 3 micrograms 5 micrograms	*Bordetella pertussis* antigens Pertussis toxoid (PT) Filamentous haemagglutinin (FHA)	 25 micrograms 25 micrograms
Hepatitis B surface antigen	10 micrograms	Hepatitis B surface antigen	10 micrograms
Poliovirus (inactivated) Type 1 (Mahoney) Type 2 (MEF-1) Type 3 (Saukett)	 40 D antigen units 8 D antigen units 32 D antigen units	Poliovirus (inactivated) Type 1 (Mahoney) Type 2 (MEF-1) Type 3 (Saukett)	 40 D antigen units 8 D antigen units 32 D antigen units
Haemophilus influenzae type b polysaccharide (Polyribosylribitol phosphate [PRP]) conjugated to meningococcal protein	3 micrograms 50 micrograms	*Haemophilus influenzae* type b polysaccharide (Polyribosylribitol phosphate [PRP]) conjugated to tetanus protein	12 micrograms 22-36 micrograms

IU=international units; MEF=Middle East Forces
See Summary of Product Characteristics for complete details of the vaccine composition.
[a] Not contained in Hexyon™.

2.2 Background

Refer to the approved labeling for detailed background information on Vaxelis™ and Hexyon™.

The primary measure to prevent the spread of diphtheria, tetanus, pertussis, polio, invasive *Haemophilus influenzae* type b disease, and hepatitis B is the implementation of comprehensive immunization programs starting in infancy and continuing throughout adolescence and adulthood, according to applicable official recommendations.

Three hexavalent pediatric vaccines are approved in the EU: Vaxelis™ (DTaP5-HB-IPV-Hib), Hexyon™ (DTaP2-HB-IPV-Hib), and INFANRIX™ hexa (DTaP3-HBV-IPV/Hib). Although the antigen composition of each vaccine is similar, there are some key differences among the 3 vaccines with respect to the pertussis and *Haemophilus influenzae* type b components (Table 1). Vaxelis™ contains 5 acellular pertussis antigens (PT, FHA, PRN, and FIM2/3), INFANRIX™ hexa contains 3 pertussis antigens (PT, FHA, and PRN), and Hexyon™ contains 2 pertussis antigens (PT and FHA). The Hib PRP is conjugated to a meningococcal outer membrane protein complex (PRP-OMPC) in Vaxelis™ and conjugated to a tetanus protein (PRP-T) in Hexyon™ and INFANRIX™ hexa. The PRP conjugation influences the kinetics and magnitude of the anti-PRP immune response during the primary series and booster dose [Decker, M.D. 1998].

Brief Summary of Diseases

Diphtheria

Diphtheria is an acute disease caused by exotoxin-producing bacterium, *Corynebacterium diphtheriae*. Transmission occurs through droplets and close physical contact [American Academy of Pediatrics 2012]. In most industrialized countries, endemic diphtheria has disappeared or become extremely rare owing to immunization [World health organization 2017]. While diphtheria is rare in infants younger than 6 months due to the presence of maternal antibody, it continues to produce substantial childhood morbidity and mortality in developing countries with low diphtheria vaccination coverage.

Tetanus

Tetanus is an infectious bacterial disease caused by *Clostridium tetani*, a ubiquitous spore forming anaerobic bacillus that can produce a potent neurotoxin, tetanospasmin. Tetanus can never be eradicated as *Clostridium tetani* spores are prevalent in the environment and may be carried in the intestinal tracts of humans and animals, though it is not transmitted from person to person [American Academy of Pediatrics 2012].

Pertussis

Pertussis (whooping cough) is caused by the bacterium *Bordetella pertussis*, transmitted from infected to susceptible individuals through droplets. Most cases of clinically recognizable pertussis occur in children 1 to 5 years of age with most severe disease occurring in young

infants, where infection can lead to hospitalization and death [World health organization 2015] [Chow, M. Y. K., et al 2016]. Despite widespread use of pertussis vaccination, young infants remain vulnerable until completion of the pertussis vaccination series.

Due to a resurgence of pertussis in many parts of the world [Tan, T., et al 2015], immunization during pregnancy is recommended in some countries [Donegan, K., et al 2014] [Centers for Disease Control and Prevention 2013]. The maternal antibody protects the vulnerable infant but does lead to blunting of the immune response to pertussis antigens in the infant [Halperin, S. A., et al 2018]. The clinical significance of the blunted immune response is unclear.

Poliomyelitis

Poliomyelitis is an acute infectious and communicable disease caused by poliovirus. Polioviruses are single-stranded RNA enteroviruses (Picornaviridae) and consist of serotypes 1, 2, and 3. Transmission is by person to person via fecal-to-oral and oral-to-oral routes. Infection is more common in infants and young children and occurs at an earlier age among children living in poor hygienic conditions [American Academy of Pediatrics 2012].

Hepatitis B

Hepatitis B infection is caused by HB virus, a member of the Hepadnaviridae family, which includes a hepatotropic group of DNA viruses. Most acute cases of HB infection in children are asymptomatic, as evidenced by the high carriage rate of serum markers in persons who have no history of acute hepatitis. The rate of acquisition of chronic infection depends largely on the mode and age of acquisition and is up to 90% in the perinatal cases [Trepo, C., et al 2014]. Among participants who successfully completed the 3-dose series, the clinical efficacy is thought to approach 100% [Van Damme, P., et al 2013] [World Health Organization 2017].

Invasive *Haemophilus influenzae* type b disease

Hib, a Gram-negative coccobacillus, is transmitted primarily by airborne droplets or by direct contact with respiratory tract secretions. The most important manifestations of Hib infection, namely meningitis, pneumonia, and other invasive diseases occur primarily in infants and toddlers aged less than 2 years [Mandell, G., et al 2010]. The disease burden is highest among infants aged 4 to 18 months. In unvaccinated populations, invasive Hib is the dominant cause of nonepidemic bacterial meningitis during the first year of life [World Health Organization 2013].

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 an investigational medicine or vaccine.

Vaccination with hexavalent vaccines (including Vaxelis™ and Hexyon™) has been shown to be beneficial and efficacious in preventing diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive disease caused by Hib. These vaccines have established safety profiles.

Participants enrolled will have previously received a 2-dose primary infant series with either Hexyon™ or Vaxelis™. All participants will receive a booster dose of Vaxelis™.

For hexavalent vaccines, a 3-dose schedule (2-dose infant primary series followed by a booster dose) is recommended in several EU countries. A mixed dose regimen of hexavalent vaccine in which Vaxelis™ is used as a booster dose after a 2-dose primary series of Hexyon™ has not previously been evaluated. However, Vaxelis™ has been evaluated as part of a mixed dose regimen in which a pentavalent vaccine was given as a part of a 3-dose series with Vaxelis™. In that study, the mixed dose regimen with Vaxelis™ was well tolerated and the immune response was acceptable for the antigens contained in the 2 vaccines [Martinon-Torres, F., et al 2017]. Vaxelis™ administered after a primary 2-dose infant series of Hexyon™ is expected to provide comparable immunogenicity and safety to a complete 3-dose regimen of Vaxelis™.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying Product Labels, and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There is no hypothesis testing in this study.

The following objectives and endpoints will be evaluated in healthy participants who were previously vaccinated with a 2-dose primary infant series of either Vaxelis™ or Hexyon™ and who will receive a booster dose of Vaxelis™ at approximately 11 to 13 months of age.

Objectives	Endpoints
Primary	
• Objective: To evaluate the safety and tolerability of a booster dose of Vaxelis™ with respect to the proportion of participants with adverse events (AEs).	• Solicited injection-site AEs from Day 1 through Day 5 postvaccination • Solicited systemic AEs from Day 1 through Day 5 postvaccination • Unsolicited AEs from Day 1 through Day 15 postvaccination • Serious adverse events (SAEs) through completion of study participation

Objectives	Endpoints
• Objective: To describe the response rates to antigens contained in both Vaxelis™ and Hexyon™ 30 days after a booster dose of Vaxelis™.	Antibody responses to: • diphtheria toxoid • tetanus toxoid • pertussis toxoid (PT) • filamentous hemagglutinin (FHA) • *Haemophilus influenzae* type b polyribosylribitol phosphate (Hib-PRP) • hepatitis B surface antigen (HBsAg) • poliovirus serotypes 1, 2, and 3 at 30 days postvaccination with Vaxelis™
Secondary	
• Objective: To describe the response rates to the pertussis antigens contained in Vaxelis™, but not in Hexyon™, 30 days after a booster dose of Vaxelis™.	Antibody responses to: • pertactin (PRN) • fimbriae 2/3 (FIM 2/3) at 30 days postvaccination with Vaxelis™
Exploratory	
• Objective: To describe the antigen-specific geometric mean concentrations (GMCs) at predose and 30 days post booster dose with Vaxelis™, and the proportion of participants with a ≥4-fold rise from Day 1 (predose) to 30 days post booster dose with Vaxelis™, for each antigen contained in Vaxelis™.	Antibody responses to: • diphtheria toxoid • tetanus toxoid • PT • FHA • PRN • FIM 2/3 • Hib-PRP • HBsAg • poliovirus serotypes 1, 2, and 3 at Day 1 (predose) and 30 days postvaccination with Vaxelis™

4 STUDY DESIGN

4.1 Overall Design

This is an open-label study of Vaxelis™ in healthy participants approximately 11 to 13 months of age who previously received a 2-dose primary infant series of either Vaxelis™ (Group 1: V,V,V) or Hexyon™ (Group 2: H,H,V) at 2 and 4 months of age as part of their routine vaccination. Approximately 160 participants will be enrolled in the study (80 participants in each group). A 0.5-mL intramuscular dose of Vaxelis™ (open-label) will be administered to all study participants at Visit 1 (Day 1).

Blood samples for immunogenicity will be drawn before vaccination at Visit 1 (Day 1) and at Visit 2 (Day 30 [30 days postvaccination with Vaxelis™]).

Immunogenicity endpoints will be described for Group 1 and Group 2. Response rates at 30 days after a booster dose of Vaxelis™ will be summarized using the serological thresholds that are accepted as correlates of protection against tetanus, diphtheria, hepatitis B, poliovirus, and Hib [Plotkin, S. A. 2010] [Andrews, Nick, et al 2003]. For pertussis, there are no benchmark antibody concentrations that are widely accepted as correlates of protection; therefore, the pertussis antigen endpoints are adapted from previously published standards based on assay LLOQ [Edwards, K. M. 2014].

Participants will be followed for solicited injection-site and systemic AEs from Day 1 through Day 5 postvaccination and for unsolicited AEs from Day 1 through Day 15 postvaccination, which will be collected using paper VRC (Section 8.3.3). Information for SAEs, regardless of whether the events are considered vaccine-related by the investigator, will be collected from the time consent is given through completion of participation in the study.

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

4.2 Scientific Rationale for Study Design

This study will assess the safety, tolerability, and immunogenicity of a mixed hexavalent vaccine regimen in which the 2-dose primary infant series is completed with Vaxelis™ or Hexyon™ and is boosted with Vaxelis™ (Dose 3). Data from this study will support the safety, tolerability, and immunogenicity of switching to Vaxelis™ after a 2-dose primary infant series with another hexavalent vaccine. This study will be conducted in healthy participants approximately 11 to 13 months of age. Although both a 2-dose and 3-dose primary series are approved in the EU, the 2-dose primary series (2 + 1 schedule) has been adopted in increasing frequency by many countries and thus chosen for the study.

It is recommended to use the same vaccine to complete a series. However, in clinical practice, switching between childhood hexavalent vaccines is sometimes necessary, which results in a “mixed” vaccine schedule. In this setting, it is recommended to complete the

primary series with 1 vaccine and limit the switch to the booster dose [Obando-Pacheco, P., et al 2018]. It is important to ensure that antibody responses are boosted (for tetanus, diphtheria, hepatitis B, poliovirus, and Hib) or completed (for pertussis) when the primary series is followed by an alternate vaccine containing similar antigens as in this study design.

Using Hexyon™ for the primary series in the mixed schedule provides the opportunity to examine the immunogenicity of a primary series of a PRP-T containing hexavalent vaccine followed by a booster dose of a PRP-OMPC containing vaccine.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

Primary Endpoints

Serum from study participants will be used to measure the immune responses to the antigens contained in both Vaxelis™ and Hexyon™ at 30 days postvaccination with Vaxelis™ (Table 2).

The endpoints used to evaluate the immune responses to the antigens contained in Vaxelis™ and Hexyon™ are consistent with established protective and acceptable antibody levels [Plotkin, S. A. 2010] [Andrews, Nick, et al 2003]. For pertussis, there are no benchmark antibody concentrations that are widely accepted as correlates of protection; therefore, the pertussis antigen endpoints are based on adaptations of previously published standards related to assay LLOQ [Edwards, K. M. 2014].

Table 2 List of Primary Endpoints

Antigen	Endpoint
Diphtheria toxoid	% ≥0.1 IU/mL
Tetanus toxoid	% ≥0.1 IU/mL
PT	% vaccine response[a]
FHA	% vaccine response[a]
Hib-PRP	% ≥1.0 µg/mL
HBsAg	% ≥10 mIU/mL
Poliovirus 1	% Nab ≥1:8 dilution
Poliovirus 2	% Nab ≥1:8 dilution
Poliovirus 3	% Nab ≥1:8 dilution

FHA=filamentous hemagglutinin; Hib=*Haemophilus influenzae* type b; HBsAg=hepatitis B surface antigen; IU=international unit; LLOQ=lower limit of quantitation; Nab=neutralizing antibodies; PRP=polyribosylribitol phosphate; PT=pertussis toxoid

[a] The pertussis vaccine response is defined as follows:
1) If prevaccination <LLOQ, then postvaccination should be ≥4 × the LLOQ.
2) If prevaccination ≥LLOQ but <2 × the LLOQ, then postvaccination should achieve a 4-fold rise (postvaccination/prevaccination ≥4).
3) If prevaccination ≥2 × the LLOQ, then postvaccination should achieve a 2-fold response (postvaccination/prevaccination ≥2).

Secondary Endpoints

Serum from study participants will be used to measure the immune responses to the pertussis antigens contained in Vaxelis™ at 30 days postvaccination with Vaxelis™ (Table 3).

Table 3 List of Secondary Endpoints

Antigen	Endpoint
PRN	% vaccine response[a]
FIM 2/3[b]	% vaccine response[a]

FIM=fimbriae; LLOQ=lower limit of quantitation; PRN=pertactin

[a] The pertussis vaccine response is defined as follows:

1) If prevaccination <LLOQ, then postvaccination should be ≥4 × the LLOQ.

2) If prevaccination ≥LLOQ but <2 × the LLOQ, then postvaccination should achieve a 4-fold rise (postvaccination/prevaccination ≥4).

3) If prevaccination ≥2 × the LLOQ, then postvaccination should achieve a 2-fold response (postvaccination/prevaccination ≥2).

[b] Antibodies to FIM 2 and FIM 3 are measured together.

4.2.1.2 Safety Endpoints

The safety endpoints evaluated in this study were selected based on the product's safety profile shown in previous studies, and guidance from regulatory agencies during product development. The VRC used to record AEs during the postvaccination periods, as defined in Section 8.1.9, was structured as recommended in the European Medicines Agency Committee on Human Medicinal Products: Guideline on Clinical Evaluation of Vaccines [European Medicines Agency 2018]. Details on the safety endpoints evaluated in this study can be found in Section 8.3.3 and Section 9.4.2. Details on AEs, including definitions and reporting requirements, can be found in Appendix 3.

4.3 Justification for Dose

The 0.5 mL dose of Vaxelis™ is approved for use in children from 6 weeks of age administered as a 2- or 3-dose primary series and a booster dose at least 6 to 12 months following the last priming dose according to national recommendations. Participants in this study had previously received a 2-dose primary series of Vaxelis™ or Hexyon™ according to national recommendations.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, 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.

5 STUDY POPULATION

Healthy male and female participants approximately 11 to 13 months of age, (≥327 days to ≤396 days inclusive) will be enrolled in this study.

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:

Type of Participant and Disease Characteristics

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

2. Has received a 2-dose infant primary series of either Vaxelis™ or Hexyon™ at approximately 2 and 4 months of age (based on a review of medical history), respectively.

Demographics

3. Is male or female, from approximately 11 months to 13 months of age (≥327 days to ≤396 days) inclusive, at the time of obtaining the informed consent.

Informed Consent

4. A legally acceptable representative has provided documented informed consent for the study.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has a known or suspected impairment of immunological function.
2. Has known or history of functional or anatomic asplenia.
3. Has a known hypersensitivity to any component of the study vaccine.
4. Has a known or suspected blood dyscrasia, leukemia, lymphoma of any type or other malignant neoplasm affecting the hematopoietic and lymphatic system.
5. Has a bleeding disorder contraindicating intramuscular vaccination.
6. Has a history of Hib, hepatitis B, diphtheria, tetanus, pertussis, or poliovirus infection.
7. Was born to a mother with a known history of hepatitis B infection.
8. *Had a recent febrile illness (defined as rectal temperature ≥38.1°C [≥100.5°F] or axillary temperature ≥37.8°C [≥100.0°F]) occurring at or within 72 hours prior to receipt of study vaccine.
9. Has encephalopathy of unknown etiology, occurring within 7 days following prior vaccination with a pertussis containing vaccine.
10. Has an uncontrolled neurologic disorder or uncontrolled epilepsy.
11. Has a health or developmental disorder that, based on the clinical judgment of the investigator, could affect evaluation of the vaccine.

Prior/Concomitant Therapy

12. Has received or is expected to receive immunosuppressive agents during the conduct of the study.
13. *Meets 1 or more of the following systemic corticosteroid exclusion criteria:

    a. Has received systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg) for ≥14 consecutive days and has not completed treatment at least 30 days before study entry.

    b. Has received any systemic corticosteroids within 14 days before study vaccination.

    c. Is expected to require any systemic corticosteroids during conduct of the study.

    Note: Topical, ophthalmic, and inhaled steroids are permitted.

14. *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 prior to Visit 2 blood draw.

    Exception: Participant may receive nonstudy pediatric licensed non-live vaccines on same day as study vaccine is given (Day 1).

    Exception: Non-live influenza vaccine may be administered, but must be given at least 7 days before receipt of study vaccine or at least 15 days after receipt of study vaccine.

15. *Has received any licensed live vaccine within 30 days before receipt of study vaccine or is scheduled to receive any live vaccine prior to Visit 2 blood draw.

16. *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

17. *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 previously or currently enrolled in a COVID-19 vaccine clinical study, or enrolled in observational studies may be included; these should be reviewed on a case-by-case basis for approval by the Sponsor.

Diagnostic Assessments

None.

Other Exclusions

18. 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, Visit 1 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 whose legally acceptable representative provides consent to participate in the clinical study, but are not subsequently enrolled 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 (Vaxelis™) 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 interventions to be used in this study are outlined in Table 4.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength	Dosage Level	Route of Admin.	Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Group 1: V,V,V	Experimental	Vaxelis™	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1	Experimental	IMP	Central
Group 2: H,H,V	Experimental	Vaxelis™	Biological/ Vaccine	Sterile Suspension (Prefilled Syringe)	Refer to product labeling	0.5 mL	IM	Single dose at Visit 1	Experimental	IMP	Central

Admin.=administration; EEA=European Economic Area; H=Hexyon™; IM=intramuscular; IMP=investigational medicinal product; mL=milliliter; NIMP=noninvestigational medicinal product; V=Vaxelis™

The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the 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 4 will be provided per the "Sourcing" column depending on 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.

6.1.1 Medical Devices

Drug-device combination product(s), which is legally marketed and provided for use in this study are: Vaxelis™ prefilled syringes. Refer to Section 8.4.8 and Appendix 4 for reporting events associated with these devices.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 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 a single dose of Vaxelis™ 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. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. 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 on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Nonstudy pediatric vaccines are permitted to be administered according to local recommended schedule, regional, and/or country guidelines, and according to the restrictions outlined in Section 5.2.

It is recommended that Vaxelis™ be administered in the right thigh. To avoid any confounding results, nonstudy injectable vaccines should not be administered in the same limb as Vaxelis™. Documentation of which limb was used for the administration of Vaxelis™ should be recorded on the appropriate eCRF. As the study is reporting injection-site AEs for Vaxelis™ (and not from nonstudy pediatric vaccines), this information should also be recorded on the paper VRC to inform the participant's legally acceptable representative of the appropriate limb to monitor for AEs related to the Vaxelis™.

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

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 after 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 before 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 8.1.10. 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 used 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 be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Approximately 5 mL of blood will be drawn at Visit 1 and Visit 2 for immunogenicity assays. The maximum amount of blood collected from each participant over the duration of the study will not exceed 10 mL.

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

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this 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 documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, 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 form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent 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.

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 documented informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

At the Day 1 visit, the participant's medical history from birth through Day 1, will be obtained by the investigator or qualified designee. This will include a question regarding the receipt of a maternal pertussis vaccine during pregnancy (see Section 2.2).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review and record any prior medications and vaccinations taken by the participant within 30 days before study vaccination.

In addition, the receipt of prior Vaxelis™ and Hexyon™ vaccinations, and monovalent hepatitis B vaccine or any other hepatitis B based combination vaccine will be recorded from birth through Day 1.

A participant who received any of the prior medications or vaccinations prohibited in the exclusion criteria (Section 5.2) should not be enrolled into the study.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

If a medical condition requires the use of a prohibitive 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.

It is important to record any analgesic or antipyretic use that occurs on the day of vaccination on the paper VRC and appropriate eCRF. Concomitant medications taken after Visit 1 and

nonstudy vaccines received since Visit 1 will be recorded in the paper VRC as specified in Section 8.3.3.

The administration of nonstudy pediatric vaccines during the study should be recorded on the appropriate eCRF. To avoid any confounding results, concomitant injectable vaccines should not be administered in the same limb as Vaxelis™. Documentation of which limb was used for the administration of Vaxelis™ must be recorded on the paper VRC (Section 8.1.9 and Section 8.3.3) and appropriate eCRF.

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 before allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused 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 in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

Adequate treatment provision, including epinephrine and equipment for maintaining an airway, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

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.

Study vaccine will be administered as specified in Section 1.3. It is recommended that Vaxelis™ be administered in the right thigh.

Observing Participants After Vaccination

All participants will be observed by study personnel for at least 15 minutes after study vaccination for any untoward effects, including allergic reactions. The observation period can be extended if clinically indicated. This observation period will be documented in the participant's study chart.

Vaccination information, such as time of vaccination and the location of the vaccine administered, must be recorded on the appropriate eCRF as per the data entry guidelines.

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 >72 hours prior to vaccination (Section 1.3).

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

8.1.9 Vaccination Report Card

The paper VRC used to record AEs during the postvaccination periods, was structured as recommended in the European Medicines Agency Committee on Human Medicinal Products: Guideline on Clinical Evaluation of Vaccines [European Medicines Agency 2018].

Body temperatures, injection-site reactions, vaccine-specific complaints, other complaints or illnesses, and concomitant medications or nonstudy vaccinations will be recorded on the VRC as described in Section 1.3 and Section 8.3.3. On Day 5, the study coordinator will remind the participant's legally acceptable representative to complete the VRC entry. The investigator or delegate will review the data captured on the VRC with the participant's legally acceptable representative as indicated in Section 1.3.

For the AEs outlined above, the investigator will use the information provided by the participant's legally acceptable representative both on the VRC, and verbally at the time of VRC review, to apply the appropriate assessment of intensity as described in Appendix 3.

8.1.10 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 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.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.12 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 the immune responses to the antigens summarized in Table 2 and Table 3 using the assays provided below.

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

8.2.1 Anti-Diphtheria Toxoid, Tetanus Toxoid, and Pertussis Antigen Serology Assay

The Meso Scale Discovery Electrochemiluminescence is a multiplexed serological assay that allows for the simultaneous quantification of human antibodies to diphtheria toxoid, tetanus toxoid, and pertussis antigens (PT, FHA, PRN, and FIM). In this assay, each well of a 96-well microtiter plate is precoated in precise positions with the 6 different antigens in a multispot fashion. Following incubation with serum samples, antigen-specific antibodies bind to the respective antigens. The captured antibodies are then detected using a sulfotag conjugated anti-human IgG conjugate. Electrical stimulation of the conjugate in the presence of a chemiluminescent substrate results in the generation of a light signal from each specific spot that is captured by a camera in relative light units. The signal generated is directly proportional to the amount of antibodies present in the sample, which is quantified using software and based on an established reference standard sample curve. The LLOQ for diphtheria antibody is 0.005 IU/mL, for tetanus antibody is 0.01 IU/mL, and for each pertussis antibody is 2.00 EU/mL.

8.2.2 *Haemophilus Influenza* Type b IgG ELISA

The Hib IgG ELISA for the in-vitro measurement of specific IgG antibodies against Hib capsular polysaccharide in human serum uses the Vacczyme™ Human Anti-Haemophilus influenzae Type b Enzyme Immunoassay Kit purchased from The Binding Site (catalog # MK016), which was further validated for use in clinical studies. The kit contains microtiter wells precoated with Hib polysaccharide antigen conjugated to human serum

albumin. Diluted serum is added to the microtiter wells and allowed to incubate. After incubation and washing to remove non-bound serum proteins, HRP-conjugated rabbit anti-human IgG is added, which binds to any captured Hib-specific IgG molecules. After another wash step, tetramethylbenzidine substrate is added; the ensuing color development reaction is then stopped at a defined time point by the addition of a dilute acid solution. The OD is measured at 450 nm and is directly proportional to the amount of anti-Hib IgG present in the serum specimen. Levels of anti-Hib IgG are quantified by interpolation from a standard curve that has been calibrated to the FDA lot 1983 reference serum.

8.2.3 Hepatitis B Enhanced Chemiluminescence (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. A HRP-labeled HBsAg conjugate (ad and ay subtypes) then forms a complex with the bound anti-HBs, forming an “antigen sandwich”. Unbound materials are removed by washing. A reagent that contains luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent increases the level and duration of the light produced. The amount of HRP conjugate bound and subsequent light produced is 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, are used to monitor the performance of the assay. These pools are each prepared from 4 individual human immune sera obtained from an external vendor. Additionally, there are anti-HBs positive and negative manufacturer-supplied controls, which are prepared from freeze-dried recalcified human plasma. The hepatitis B WHO International reference standard at 10 mIU/mL is also run as a control in every assay. The LLOQ of the assay is 5 mIU/mL.

8.2.4 Poliovirus Neutralization Assay

Anti-poliovirus types 1, 2, and 3 will be measured by neutralization assay. Serial dilutions of sera are mixed with challenge poliovirus and incubated with cultured Vero cells that are sensitive to poliovirus. Specific neutralizing antibodies contained in the sera bind to and neutralize the challenge poliovirus. The neutralized poliovirus does not affect cellular viability, and these cells continue to metabolize and release CO_2, reducing the pH of the culture medium. Cell survival correlates with the change in the pH indicator (phenol red to yellow at pH $\leq$7.0) contained in the medium. In the absence of neutralizing antibodies, the challenge poliovirus reduces cellular metabolism and CO_2 production. Therefore, the pH does not decrease and a color change is not detected. The poliovirus mouse inoculation test measures the functional serum antibody response to poliovirus by utilizing Vero cells

(African green monkey kidney cells) and wild type poliovirus strains 1, 2, and 3 (Mahoney, MEF-1, and Saukett, respectively) as the challenge virus. The Karber method is used to determine the serum dilution that neutralized 50% of the challenge virus. Results are expressed as titers (1:dilution). The LLOQ for each of the antibodies to poliovirus types 1, 2, and 3 assays is 1:4.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) at Day 1 for all participants. Any clinically significant abnormality will be recorded on the appropriate eCRF.

The complete physical examination procedures include obtaining vital signs (heart rate, respiratory rate, and rectal temperature), auscultation of the heart and lung, examination of the abdomen, and an assessment of the head, eyes, ears, nose and throat, skin, lymph nodes, neurological system, and musculoskeletal system.

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

8.3.2 Body Temperature Measurement

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

The participant's legally acceptable representative will be asked to record the participant's temperature reading on the VRC from Day 1 through Day 5 postvaccination.

Rectal is the preferred method of obtaining participant's temperature. Axillary (underarm) is an acceptable method, but temperature needs to be confirmed by rectal measurement if the axillary temperature is reported to be ≥37.8°C (≥100.0°F). In this case, both axillary and rectal temperatures must be recorded on the VRC. 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 Safety Assessment and Use of the VRC

All participants will be observed for at least 15 minutes postvaccination for any immediate reactions. If any immediate AEs are observed during this period, the time at which the event

occurred within this timeframe, as well as the event itself, any concomitant medications that were administered, and resolution of the event, must be recorded on the appropriate eCRF.

The limb that was used for the administration of study vaccine will be recorded in the VRC (Note: the study will report injection-site AEs from study vaccine only [not for nonstudy vaccines]; the location of study vaccine administration should be used by the participant's legally acceptable representative to monitor the appropriate limb for injection-site AEs related to study vaccine).

Participant's legally acceptable representative will use the VRC (Section 8.1.9) to document the following information:

- Body temperatures measured Day 1 (day of vaccination) to Day 5 postvaccination
- Solicited injection-site AEs (see Section 8.4.9.1) Day 1 to Day 5 postvaccination
- Solicited systemic AEs (see Section 8.4.9.1) Day 1 to Day 5 postvaccination
- Any other unsolicited injection-site or systemic AEs (see Section 8.4.9.2) Day 1 to Day 15 postvaccination
- Use of any analgesic or antipyretic on the day of vaccination
- Concomitant medications and nonstudy vaccinations Day 1 to Day 15 postvaccination

8.3.4 Clinical Safety 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 an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, 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 an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity 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 participant provides documented informed consent, but before the receipt of allocation number, 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.

All AEs that occur from the time of allocation through 15 days postvaccination, must be reported by the investigator. All SAEs and other reportable safety events that occur from the time of allocation throughout the duration of the individual's participation in the study, must be reported by the investigator, regardless of whether the events are considered to be vaccine-related by the investigator.

Investigators are not obligated to actively seek AEs 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 AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated Table 5.

Table 5 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 all	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	Not applicable since participants are infants.			
Event of Clinical Interest	There are no events of clinical interest for this study.			Not applicable
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

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 AEs 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 AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including 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 nonserious AEs 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

Information in this section is not applicable since participants are infants.

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

This is not applicable to this study.

8.4.7 Events of Clinical Interest

There are no events of clinical interest for this study.

8.4.8 Medical Device and Drug-device Combination Products - PQCs/Malfunctions

The method of documenting and reporting of such events (complaints associated with medical devices, including PQCs/malfunctions) will occur as below and in Appendix 4.

To fulfill regulatory reporting obligations worldwide, medical device information associated with AEs will be collected and reported to the Sponsor in the same time frame as AEs per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines.

PQCs/malfunctions including those that involve a participant or any user/associated person must be reported to the Sponsor. Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities about certain safety information relating to medical devices and drug-device combination products being used in clinical studies.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality between the AE and the medical device or device constituent of combination product.

8.4.9 Adverse Events on the VRC

Participant's legally acceptable representative will use a paper VRC to report solicited and unsolicited AEs.

The definitions of solicited and unsolicited AEs can be found in Appendix 3.

8.4.9.1 Solicited Adverse Event

Solicited AEs for this study are summarized in Table 6.

Table 6 Solicited Adverse Events

Type of Solicited Adverse Event	**Predefined Solicited Adverse Events (Preferred Term)**	**Solicited Time Period**
Injection-site	Injection-site swelling Injection-site redness (erythema) Injection-site pain or tenderness (pain)	Day 1 through Day 5 postvaccination
Systemic	Vomiting Drowsiness (somnolence) Appetite lost (decreased appetite) Irritability	Day 1 through Day 5 postvaccination

All solicited injection-site AEs will be considered related to study intervention.

In addition, the investigator will review all solicited AEs for the following:

- Is the event a symptom of another diagnosis?
- Is the event ongoing at the end of the solicited period?
- Does the event meet serious criteria?

A solicited AE that meets any of the above criteria must also be reported on the appropriate eCRF as specified in the data entry guidelines.

8.4.9.2 Unsolicited Adverse Events

Unsolicited AEs for this study are events that are 1) not predefined in Table 6 or 2) predefined in Table 6, but reported at any time outside the solicited time period.

As detailed in Section 8.4, the investigator will assess unsolicited AEs that meet the definition of an AE or SAE with respect to seriousness, intensity, and causality.

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 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

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

8.11 Visit Requirements

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

8.11.1 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.

8.11.2 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 statistical analysis plan are summarized below; the comprehensive plan is provided in Section 9.2 to 9.12.

Study Design Overview	A Phase 4, Open-label, Multicenter, Study to Evaluate the Safety, Tolerability, and Immunogenicity of Vaxelis™ in Healthy Participants Previously Vaccinated With a 2-Dose Primary Infant Series of Either Vaxelis™ or Hexyon™
Treatment Assignment	Approximately 160 participants will be enrolled at ~11 to 13 months of age who have previously received a 2-dose primary infant series of either Vaxelis™ or Hexyon™. Group 1: V,V,V ≈ 80 participants, Group 2: H,H,V ≈ 80 participants. Participants in both groups will receive Vaxelis™ as their booster vaccination.
Analysis Populations	Immunogenicity: Per-protocol (PP) Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	**Immunogenicity:** The following antibody responses will be measured at 30 days postvaccination with Vaxelis™ as primary endpoints: • diphtheria toxoid • tetanus toxoid • pertussis toxoid (PT) • filamentous haemagglutinin (FHA) • *Haemophilus influenae* type b polyribosylribitol phosphate (Hib-PRP) • hepatitis B surface antigen (HBsAg) • poliovirus serotypes 1, 2, and 3 **Safety:** • solicited injection-site adverse events (AEs) from Day 1 through Day 5 postvaccination • solicited systemic AEs from Day 1 through Day 5 postvaccination • unsolicited AEs from Day 1 through Day 15 postvaccination • Serious adverse events (SAEs) through completion of study participation
Key Secondary Endpoints	The following antibody responses will be measured at 30 days postvaccination with Vaxelis™ as secondary endpoints: • pertactin (PRN) • fimbriae 2/3 (FIM 2/3)
Statistical Methods for Key Immunogenicity Analyses	No statistical hypothesis testing will be performed for immunogenicity analyses. For the immunogenicity endpoints, the response rates to each antigen in Vaxelis™ and the corresponding 95% confidence intervals (CIs) will be provided, for each group.
Statistical Methods for Key Safety Analyses	The overall safety endpoints and specific AEs will be summarized by providing the number and percentage of participants with AEs. The 95% within-group CIs for the percentages of participants with the event will be provided.

Interim Analyses	No interim analyses are planned.
Multiplicity	No multiplicity adjustment is needed for the primary immunogenicity objective as there is no hypothesis testing.
Sample Size and Power	This study will enroll approximately 160 participants (80 in each group), which will allow estimation of the primary immunogenicity endpoints with a reasonable 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 nonrandomized, 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; no hypothesis testing will be performed.

9.4 Analysis Endpoints

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

9.4.1 Immunogenicity Endpoints

The primary immunogenicity endpoints include the response rates, ie, proportions of participants with antibody-specific responses to the following antigens at 30 days postvaccination with Vaxelis™:

- Diphtheria toxoid (% ≥0.1 IU/mL)
- Tetanus toxoid (% ≥0.1 IU/mL)
- PT (% vaccine response)
- FHA (% vaccine response)
- Hib-PRP (% ≥1.0 µg/mL)
- HBsAg (% ≥10 mIU/mL)
- Poliovirus 1 (% Nab ≥1:8 dilution)

- Poliovirus 2 (% Nab ≥1:8 dilution)
- Poliovirus 3 (% Nab ≥1:8 dilution)

The secondary immunogenicity endpoints include the response rates, ie, proportion of participants with antibody-specific responses to the following antigens at 30 days postvaccination with Vaxelis™:

- PRN (% vaccine response)
- FIM 2/3 (% vaccine response)

The response thresholds for the antigens in the primary and secondary immunogenicity endpoints are defined in Table 2 and Table 3 in Section 4.2.1.1.

The exploratory endpoints include the antibody-specific GMCs for all antigens contained in Vaxelis™ on Day 1 (predose) and 30 days postvaccination with Vaxelis™, and the proportion of participants with a ≥4-fold rise in antibody level from Day 1 to Day 30 for each antigen.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and postvaccination temperature measurements after vaccination with Vaxelis™.

The safety endpoints include:

- Number of participants with solicited injection-site AEs (swelling, redness/erythema, tenderness/pain) from Day 1 through Day 5 postvaccination with Vaxelis™.
- Number of participants with solicited systemic AEs (vomiting, drowsiness/somnolence, appetite lost/decreased appetite, and irritability) from Day 1 through Day 5 postvaccination with Vaxelis™.
- Number of participants with unsolicited AEs from Day 1 through Day 15 postvaccination with Vaxelis™.
- Number of participants with an SAE, a vaccine-related SAE, discontinuation due to an AE, and death, from Day 1 through completion of study participation.
- Participants body temperature measured from Day 1 through Day 5 postvaccination with Vaxelis™.

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The PP population will serve as the population for the analysis of immunogenicity data. 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, but are not limited to:

- Failure to receive study vaccine at Visit 1 (Day 1).
- Receipt of a prohibited medication or prohibited vaccine (as defined in Section 5.2) within the study window.
- Collection of blood sample at Visit 2 outside the prespecified window (Day 26 to Day 40).

The final determination on important protocol deviations, and thereby the composition of the PP population, will be made prior to the final database lock and will be documented in a separate memo.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all participants who received study vaccination.

At least 1 temperature measurement obtained after study intervention is required for inclusion in the analyses of temperature.

9.6 Statistical Methods

9.6.1 Statistical Methods for Immunogenicity Analyses

No statistical hypothesis testing will be performed for immunogenicity analyses.

The primary and secondary immunogenicity objectives will be evaluated by computing the proportion of participants with antibody responses for each antigen, detailed in Section 4.2.1.1, at 30 days postvaccination with Vaxelis™. Point estimates and 95% CIs will be provided by group (Group 1: V,V,V and Group 2: H,H,V) for both primary and secondary endpoints. The CIs will be calculated based on the exact binomial method proposed by Clopper and Pearson [CLOPPER, C. J. and PEARSON, E. S. 1934].

The analyses for the exploratory endpoints will be described in sSAP.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and postvaccination temperatures.

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary of the number and percentage of participants within each group with at least 1 AE, vaccine-related AE, SAE, vaccine-related SAE, a discontinuation from the study due to an AE, and an AE resulting in death. Point estimates and 95% within-group CIs for the percentages of participants with the event will be provided (Table 7).

The number and percentage of participants with solicited injection-site AEs from Days 1 to 5 postvaccination, solicited systemic AEs from Days 1 to 5 postvaccination, unsolicited AEs from Days 1 to 15 postvaccination, maximum temperatures from Days 1 to 5 postvaccination, and AEs by SOC will also be provided. For all AEs, point estimates and 95% within-group CIs for the percentages of participants with the event will be provided regardless of the number of participants with the event (Table 7).

Within-group CIs will be calculated based on the exact binomial method proposed by Clopper and Pearson [CLOPPER, C. J. and PEARSON, E. S. 1934]. CIs should only be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance.

Table 7 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Within-group CI
Overall Safety Assessment	Solicited injection-site swelling (Days 1 through 5)	X	X
	Solicited injection-site redness/erythema (Days 1 through 5)	X	X
	Solicited injection-site tenderness/pain (Days 1 through 5)	X	X
	Solicited vomiting (Days 1 through 5)	X	X
	Solicited drowsiness/somnolence (Days 1 through 5)	X	X
	Solicited appetite lost/decreased appetite (Days 1 through 5)	X	X
	Solicited irritability (Days 1 through 5)	X	X
	Unsolicited AEs (Days 1 through 15)	X	X
	Any AE	X	X
	Any vaccine-related AE	X	X
	Any SAE	X	X
	Any vaccine-related SAE	X	X
	Discontinuation from study due to AE	X	X
	AE that resulted in death	X	X
	SOCs	X	X
	Maximum temperature measurements (Days 1 through 5)	X	X

AE=adverse event; CI=confidence interval; SAE=serious adverse event; SOC=System Organ Class

9.6.2.2 Assessment of Safety Topics of Special Interest

There are no safety topics of special interest.

9.6.3 Demographic and Baseline Characteristics

The relevant demographic and baseline characteristics will be summarized by group. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, and prior and concomitant vaccinations and therapies will be summarized either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analyses are planned.

9.8 Multiplicity

No multiplicity adjustment is needed as there is no hypothesis testing.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

This is an estimation study. This study will enroll approximately 160 participants (80 in each group) and will allow estimation of the primary immunogenicity endpoints with a reasonable 95% CI. This is based on the following assumptions: 1) a 5% nonevaluability rate (76 evaluable participants per group), and 2) underlying response rates for Vaxelis™ following a booster dose based on the study results from V419-008 [Silfverdal, S. A., et al 2016], detailed in Table 8.

The CI was based on the exact binomial method proposed by Clopper and Pearson [CLOPPER, C. J. and PEARSON, E. S. 1934] assuming 95% evaluable participants in each group are included in the analysis.

Table 8 summarizes estimates of the CIs under various hypothetical observed response rates for specific antigens.

Table 8 Estimates of the 95% Confidence Intervals for Different Hypothetical Observed Response Rates

Sample Size (in each group)	Evaluable Sample Size (in each group)	Endpoint	Observed Response (%)	95% CI (%)
80	76	Anti-diphtheria	98	(91.8, 99.8)
		Anti-Hib-PRP	90	(80.9, 95.7)
		Anti-tetanus and all anti-pertussis	96	(88.8, 99.2)

CI=confidence interval; Hib=*Haemophilus influenza* type b; PRP=polyribosylribitol phosphate
The response rate after Vaxelis™ is assumed based on historical data.

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE 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 1.00% (1 of every 100 participants receiving the vaccine), there is an 80% chance of observing at least 1 SAE among 160 participants. If the underlying incidence of an SAE is 0.43% (1 of every 231 participants receiving the vaccine), there is a 50% chance of observing at least 1 SAE among 160 participants. If no SAEs are observed among the 160 participants, this study will provide 95% confidence that the underlying percentage of participants with SAE is <1.85% (1 in every 53 participants).

9.10 Subgroup Analyses

Subgroup analyses based on receipt of pertussis vaccine during pregnancy by the participant's biological mother (ie, received vs not received; see Section 8.1.4) will be performed for the pertussis immunogenicity endpoints. Details of subgroup analyses will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

Given that participants will receive just a single dose of Vaxelis™ during the study, compliance will not be calculated. However, the number and proportion of participants vaccinated with Vaxelis™ will be summarized (Section 9.12).

9.12 Extent of Exposure

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

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 & Dohme LLC, Rahway, NJ, USA (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. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. 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.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

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 potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are 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, as well as all applicable data protection rights. 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, frequently 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 before 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 ICMJE 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 trials 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, ICH 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 participants' documented informed consent, 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 preexisting 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.
- 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a VRC and that is communicated by a participant/participant's legally authorized representative who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Solicited AEs are predefined local (at the injection/administration site) and systemic events for which the participant/participant's legally authorized representative is specifically questioned, and which are noted by the participant/participant's legally authorized representative in their VRC.

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 preexisting condition that has not worsened is not an SAE.) A preexisting 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 and SAE recording

- When an AE/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 AE/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 AE/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 AE 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 with a legally acceptable representative: awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies with a legally acceptable representative: 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 with a legally acceptable representative: extremely distressed or unable to do usual activities).

- Injection-site erythema/redness or swelling from the day of vaccination through Day 5 postvaccination will be evaluated by maximum size instead of intensity. After Day 5 , these events will be evaluated by intensity as described above.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE 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 AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; 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 AE:

    - **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 AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a vaccine-induced effect?

    - **Likely Cause:** Is the AE 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 AE 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 AE 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 AE 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 AE onset relative to the administration of the Sponsor's product is reasonable. The AE 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 AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/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 AE 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 AE 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

AE, 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 AE Reporting 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: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

The recording and follow-up procedures described in this protocol apply to all medical devices as described below. For purposes of this section, medical devices in scope for device information collection include devices intended to be used by a study participant according to the study protocol, that are manufactured by the Sponsor or for the Sponsor by a third party, licensed by the Sponsor for human use and/or drug-device combination products as listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

10.4.1 Definitions

Combination Product - A product comprised of two or more regulated components (ie, a drug and a device; a biologic and device; a biologic and a drug; or a drug, a device, and a biologic). Combination products can be single entity, copackaged, or colabeled.

Complaint - Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. This would include PQC, AE, and customer feedback.

A complaint does not necessarily need to involve a user or any other person.

Constituent Part - A drug, device, or biological product that is part of a combination product.

Customer Feedback - A report that does not allege a PQC or defect and has no relevant safety information/untoward event associated with it (eg, goodwill or courtesy replacement, consumer preference or suggestion, remark which may suggest an improvement in the functionality or quality of a medical device or device-like features of a drug delivery system).

Malfunction - The failure of a device to meet its performance specifications or otherwise perform as intended.

Medical Device - Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the MANUFACTURER to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

PQC - Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by external customers. This includes potential device or device component malfunctions. Note: A report of Lack or Limited Efficacy is considered an AE rather than a PQC.

Serious Injury - An injury or illness that:

1. Is life-threatening,

2. Results in permanent impairment of a body function or permanent damage to a body structure, or

3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

10.4.2 Recording, Assessing Causality, and Follow-up of PQCs/Malfunctions

Recording

- When a Complaint including PQC/malfunction occurs it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- Events occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines. Medical device/device constituent part of drug device combination product information will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor.

Assessing Causality

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.

- The investigator will use clinical judgement to determine the relationship.

- Alternative causes such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration should be considered and investigated.

Follow-up

- The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

10.5 Appendix 5: Contraceptive Guidance

Not applicable.

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
APaT	All Participants as Treated
CI	confidence interval
CO_2	carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CRF	Case Report Form
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
DTaP-HB-IPV-Hib	diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and *Haemophilus influenzae* type b conjugate vaccine (adsorbed)
ECi	enhanced chemiluminescence
eCRF	electronic Case Report Form
EDC	electronic data collection
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
EU/mL	ELISA units per milliliter
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FHA	filamentous haemagglutinin
FIM 2/3	Fimbriae types 2 and 3
GCP	Good Clinical Practice
HB	hepatitis B
HBsAg	hepatitis B surface antigen
Hib	*Haemophilus influenza* type b
HRP	horseradish peroxidase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IRB	Institutional Review Board
IU/mL	International units per milliliter
LLOQ	lower limit of quantitation
Nab	neutralizing antibodies
OD	optical density
PP	per-protocol

Abbreviation	Expanded Term
PQC	product quality complaint
PRN	pertactin
PRP	polyribosylribitol phosphate
PT	pertussis toxoid
RNA	ribonucleic acid
SAE	serious adverse event
SoA	schedule of activities
SOC	system organ class
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
VRC	Vaccination Report Card
WHO	World Health Organization

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