NCT04398706

Safety and Immunogenicity of a Pneumococcal Conjugate Vaccine when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Toddlers and Infants

Phase II, randomized, observer-blind, controlled, age de-escalation study in approximately 140 toddlers and 700 infants in the US, Canada and Honduras.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	PSK00008
Development Phase:	Phase II
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, US
Investigational Product(s):	Pneumococcal Conjugate Vaccine
Form / Route:	Liquid / Intramuscular (IM)
Indication For This Study:	PCV 21 as a single dose in toddlers aged 12 to 15 months and as 4 doses in infants at 2, 4, 6, and 12 to 15 months of age
Version and Date of the SAP core body part:	Version 3.0 05 May 2022

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List of Abbreviations

Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CI	confidence interval
CRB	(electronic) case report book [all the case report forms for a participant]
CSR	clinical study report
D	day
DC	diary card
DMC	Data Monitoring Committee
dil	dilution
DTaP	diphtheria, tetanus, and acellular pertussis
ECL	electro-chemiluminescence assay
ELISA	enzyme linked immunosorbent assay
ESDR	early safety data review
EU	endotoxin units
FAS	full analysis set
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
GM	geometric mean
GMC	geometric mean concentration
GMCR	geometric mean concentration ratio
GMT	geometric mean titer
GMTR	Geometric mean titer ratio
HB	hepatitis B
Hib	*Haemophilus influenza b*
IgA	immunoglobulin type A
IgG	immunoglobulin type G
IU	international unit
IRT	interactive response technology
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mIU	mili-international units
MOPA	Multiplexed opsonophagocytic killing assay

M-M-R	measles, mumps, rubella
NA	Not applicable
OPA	opsonophagocytic activity
PC	phone call
PCV	pneumococcal conjugate vaccine
PPAS	per-protocol analysis set
PD3	1-month post-dose 3
PD4	1-month post-dose 4
PRN	pertactin
PRP	polyribosyl-ribitol phosphate
PT	pertussis toxoid / toxin
PT	preferred term
Q1; Q2; Q3	first quartile; second quartile (median); third quartile
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SMT	Safety Management Team
SOC	system organ class (primary)
TLF	table(s), listing(s), and figure(s)
ULOQ	upper limit of quantification
Vac	vaccination
WHO	World Health Organization

1 Introduction

Sanofi Pasteur is developing a PCV21 that would extend the protection against pneumococcal disease to serotypes 8, 9N, 10A, 11A, 12F, 15B, 22F, and 33F, in addition to the 13 serotypes included in Prevnar 13® (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). These serotypes have been selected based on recent epidemiological data that showed increasing emergence in North America and in Europe.

This is a Phase II study that will evaluate the safety and immunogenicity of different formulations of a multivalent pneumococcal conjugate vaccine (PCV) administered concomitantly with routine pediatric vaccines in healthy toddlers and infants. This vaccine (henceforth referred to as SP0202) is expected to be indicated for the prevention of invasive and non-invasive disease caused by *Streptococcus pneumoniae* (or pneumococcus), in all age groups.

2 Trial Objectives

2.1 Primary Objectives

Safety

- To assess the safety profile of each SP0202 formulation and Prevnar 13 in toddlers and infants (after each and any injection)

Immunogenicity

- To assess the immune response (serotype specific IgG concentration) of the SP0202 formulations and Prevnar 13 1 month after the administration of one dose in toddlers (Groups 1 to 4)
- To assess the immune response (serotype specific IgG concentration) of the SP0202 formulations and Prevnar 13 1 month after the administration of 3 doses in infants (Groups 5 to 8)
- To assess the immune response (serotype specific IgG concentration) of the SP0202 formulations and Prevnar 13 1 month after administration of a 4-dose schedule in infants (Groups 5 to 8)

2.2 Secondary Objectives

Immunogenicity of SP0202 or Prevnar 13 vaccines

- To assess the immune response (serotype specific opsonophagocytic activity [OPA] titer) of the SP0202 formulations and Prevnar 13 1 month after the administration of one dose in toddlers (Groups 1 to 4)

- To assess the immune response (serotype specific OPA titer) of the SP0202 formulations and Prevnar 13 1 month after the administration of 3 doses in a subset of infants (Groups 5 to 8)
- To assess the immune response (serotype specific OPA titer) of the SP0202 formulations and Prevnar 13 1 month after administration of a 4-dose schedule in a subset of infants (Groups 5 to 8)

Immunogenicity of concomitant licensed vaccines when co-administered with SP0202 or Prevnar 13

Toddlers

- To describe the Ab responses against Pentacel® antigens before and 1 month following injection of Pentacel

Infants

- To describe the Ab responses against antigens of the routine pediatric vaccines (Pentacel, RotaTeq®, ENGERIX-B®, M-M-R$_{II}$®, and VARIVAX®) when administered concomitantly with either SP0202 or Prevnar 13 (at pre-Dose 1* for RotaTeq, Diphteria, Tetanus, and Pertussis antigens; at post-dose 3 [PD3] for ENGERIX-B†, RotaTeq, and Pentacel; at post-dose 4 [PD4] for M-M-R$_{II}$ and VARIVAX])

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This will be a Phase II, randomized, active-controlled, observer-blind, age de-escalating, multi-centered study to assess the safety and the immunogenicity of 3 different formulations of an investigational PCV in toddlers (12 to 15 months of age [MoA]), and infants (2 MoA). The vaccine is referred to as SP0202 in what follows.

PSK00008 study is designed to evaluate the safety and immunogenicity of SP0202 formulations in a step-down approach and will involve 2 stages (Table 3.1):

- In Stage I, toddlers aged between 12 and 15 months, who previously received the 3-dose primary series of Prevnar 13 will receive 1 dose of either one SP0202 formulation (Group 1, 2, and 3) or Prevnar 13 (Group 4), concomitantly administered with Pentacel
- In Stage II, infants aged 2 months will receive 3 doses of either one SP0202 formulation or Prevnar 13 at approximately at 2, 4, and 6 MoA and a 4th dose at 12 to 15 MoA (Groups 5, 6, 7, and 8), co-administered with pediatric vaccines recommended at this age

* Not applicable from protocol Version 5.0

† Immunogenicity to ENGERIX-B will be presented according to the number of doses received

A total of 140 toddlers (35 participants per group) will be enrolled in Stage I and randomized in a 1:1:1:1 ratio to receive a single dose of either one SP0202 formulation (Groups 1 to Group 3) or Prevnar 13 (Group 4).

A total of 700 infants (175 participants per group) will be enrolled in Stage II and randomized in a 1:1:1:1 ratio to be vaccinated with 1 of the 3 SP0202 formulations (Group 5 to Group 7) or with Prevnar 13 (Group 8) (Table 3.1).

Table 3.1: Study Design

Stage I	
Toddlers (aged 12 to 15 months)	
140 participants who have received a 3-dose primary series of Prevnar 13 and DTaP-IPV + Hib vaccines in infancy	35 participants will receive 1 dose of SP0202-IIb and 1 dose of Pentacel concomitantly (Group 1)
	35 participants will receive 1 dose of SP0202-VI and 1 dose of Pentacel concomitantly (Group 2)
	35 participants will receive 1 dose of SP0202-VII and 1 dose of Pentacel concomitantly (Group 3)
	35 participants will receive 1 dose of Prevnar 13 and 1 dose of Pentacel concomitantly (Group 4)
Stage II	
Infants (aged 2 months)	
525 participants will be randomized to receive 4 doses of one SP0202 formulation, along with routine pediatric vaccines, at 2, 4, 6, and 12-15 months of age	175 participants will receive 4 doses of SP0202-IIb (Group 5)
	175 participants will receive 4 doses of SP0202-VI (Group 6)
	175 participants will receive 4 doses of SP0202-VII (Group 7)
175 participants will receive 3 doses of Prevnar 13, along with routine pediatric vaccines, at 2, 4, 6, and 12-15 months of age	175 participants will receive 4 doses of Prevnar 13 (Group 8)

As a safety precaution, a stepwise approach for enrollment is proposed: toddlers (aged 12-15 months) will be enrolled and vaccinated. Using a diary card/electronic diary card (DC / eDC) system, blinded safety data collected through D30 after injection on at least [redacted]% of toddlers participants (Stage I) will be first reviewed internally by the Safety Management Team (SMT) and by the independent Data Monitoring Committee (DMC). An acceptable review of safety data and an acceptable safety profile based on prospectively defined criteria will be required before proceeding with the enrollment of infants (2 MoA).

For both toddlers and infants, immediate unsolicited systemic adverse events (AEs) will be collected for 30 minutes following each injection. Solicited injection site reactions will be collected between D0 and D7 after each injection for both study and concomitant pediatric vaccines. Solicited systemic reactions will be collected between D0-7 after each injection. Unsolicited AEs will be collected between D0-30 after each injection. Serious Adverse Events

(SAEs) and adverse events of special interest (AESIs)[‡] information will be collected throughout the study from V01 until the end of the study, ie, 6 months after the last injection.

Following DMC recommendations after Stage I early safety data review (ESDR), any SP0202 formulation may be excluded from entering Stage II of the study if considered not adequate for further evaluation in infants. In such a case, the number of groups to entered Stage II will be adjusted accordingly and the planned sample size in each selected group will be kept.

An Interactive Response Technology (IRT) will be used to assign participant numbers and study group at each clinical site.

Over the study period of Stage I (Group 1 to 4), toddlers will attend 2 planned visits at D0 and D30. Two blood samples (BL) of 6 mL each will be collected for the assessment of the immunogenicity of the 3 SP0202 formulations, Prevnar 13 and Pentacel: before injection of PCV (BL0001) at D0 (Visit 1 [V01]) and 1 month after PCV injection (BL0002) at D30 (V02).

Over the study period of Stage II (Group 5 to 8), infants will attend 6 planned visits at D0, D60, D120, D150, D300-390, and D330-420. Overall, 3 or 4 BL will be collected for the assessment of the immunogenicity of the 3 SP0202 formulations, Prevnar 13 and pediatric vaccines: before injection of PCV (BL0001; 3 mL) at D0 (V01)[*], 1 month after PCV Dose 3 (BL0002; 6 mL) at D150 (V04), before PCV Dose 4 (BL0003; 6 mL) at D300 (V05), and 1 month after PCV Dose 4 (BL0004; 6 mL) at D330 (V06).

The study vaccine-related immunogenicity assessments will involve both the measurement of serotype specific IgG concentrations and of OPA titers. IgG concentrations for all pneumococcal serotypes included in each of the SP0202 formulations and Prevnar 13 will be measured in all participants. The evaluation of the IgG concentrations will be made using the international standard reference serum 007sp that includes assignment for all serotypes included in SP0202. OPA will be measured in all available samples from Stage 1 and on a subset of Stage 2 samples.

The immunogenicity of the pediatric vaccines administered concomitantly with the study vaccines will be assessed using standard assays for the respective antigens.

3.2 Trial Plan

Enrollment

A total of approximately 140 participants in Stage I and 700 participants in Stage II will be enrolled. Eligible participants will be identified and recruited, in accordance with inclusion / exclusion criteria. Each participant's parent / guardian must sign and date the ICF before any procedure or treatment associated with the study is performed. A step-down approach to vaccine administration from Stage I to Stage II will be used: toddlers will first be vaccinated (Stage I) and after the safety data of at least [redacted]% of participants from Stage I has been reviewed by the SMT and by the independent DMC, the enrollment of infants will start. It is to be noted that after Stage I data review, the DMC may recommend dropping one or more SP0202 formulations before

[‡] For both toddlers and infants, anaphylaxis/hypersensitivity, convulsions (including febrile convulsions), hypotonic-hyporesponsive episode, and apnea will be considered as AESIs.

[*] Not applicable from protocol V5.0

moving to Stage II. In any cases, the sample size of each group will remain unchanged (ie, around 175 infants per group) and ratio between groups will be balanced.

Vaccination

In Stage I, toddlers aged between 12 to 15 months, will receive one dose of either one formulation of SP0202 formulation or Prevnar 13, concomitantly administered with Pentacel.

In Stage II, infants aged 2 months will receive 3 doses of either one SP0202 formulation or Prevnar 13 approximately at 2, 4, and 6 MoA and a 4th dose at 12 to 15 MoA (Groups 5, 6, 7, and 8), co-administered with pediatric vaccines recommended at this age.

All infants will receive the following routine vaccines (summarized in Table 3.2):

- Pentacel (DTaP-IPV//Hib) at 2, 4, 6 months of age. It is to be noted that the fourth Pentacel dose will be given after the completion of the last study visit. The study personnel / Investigator will be responsible for administering this dose at the recommended age as per their standard practices
- RotaTeq (pentavalent rotavirus vaccine [RV5]) at 2, 4, and 6 months of age
- M-M-R$_{II}$ (measles, mumps, rubella [MMR] vaccine) at 12 to 15 months of age
- VARIVAX (varicella vaccine) at 12 to 15 months of age
- In addition to routine vaccine mentioned above, hepatitis B vaccination (ENGERIX-B) can be administered concomitantly with Pentacel and PCV doses at V01, V02, and V03. A first dose of hepatitis B vaccine can be given at least 28 days prior to study enrollment.

Table 3.2: Injection schedule for study and pediatric vaccines in infants

Visit (V)	V01	V02	V03	V05
Approximate age (months)	2	4	6	12 to 15
PCV for Group 5, 6, and 7	SP0202 (IIb, VI, or VII)	SP0202 (IIb, VI, or VII)	SP0202 (IIb, VI, or VII)	SP0202 (IIb, VI, or VII)
Group 8	Prevnar 13	Prevnar 13	Prevnar 13	Prevnar 13
Concomitant pediatric vaccines	Pentacel* RotaTeq†	Pentacel* RotaTeq†	Pentacel* RotaTeq†	M-M-R$_{II}$ + VARIVAX§
	ENGERIX-B‡	ENGERIX-B‡	ENGERIX-B‡	

* Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and *Haemophilus* b Conjugate [Tetanus Toxoid Conjugate]; Sanofi Pasteur Ltd)

† RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent); Merck & Co, Inc.

‡ ENGERIX-B (Purified Recombinant Hepatitis B Surface Antigen; GlaxoSmithKline Inc.). Hepatitis B vaccination can be administered concomitantly with Pentacel and PCV doses at V01; V02 and V03. A first dose of hepatitis B vaccine can be given at least 28 days prior to study enrollment.

§ M-M-R$_{II}$ (Measles, Mumps, and Rubella Virus Vaccine Live) and VARIVAX® (Varicella Virus Vaccine Live); Merck & Co, Inc.

Additionally, based on the immunogenicity results, a rescue dose of Prevnar 13 will be recommended for any participant that will receive one of the 3 formulations of SP0202 vaccine and that will meet the following criteria:

- Any toddler in Stage I of the study with serotype specific pneumococcal IgG antibody concentration < 0.35 µg/mL for 4 or more serotypes in common between SP0202 vaccine and Prevnar 13 at 1-month post-vaccination.
- Any infant in Stage II of the study with serotype specific pneumococcal IgG antibody concentration < 0.35 µg/mL for 4 or more serotypes in common between SP0202 vaccine and Prevnar 13 at 1-month post-dose 3.

The rescue dose of Prevnar 13 should be given as soon as possible after the immunogenicity results will be available for toddlers, or as soon as possible after the immunogenicity results of the fourth dose of SP0202 vaccine for infants. This rescue dose will be given outside of the protocol visit.

Blood sampling

During Stage I, all toddlers will provide 2 BL of 6 mL each for the assessment of the immunogenicity of the 3 SP0202 formulations, Prevnar 13 and Pentacel: a first sample (BL0001) before injection at D0 (V01) and a second sample (BL0002) at D30 (+14 days) post-injection (V02).

During Stage II, all infants will provide 3 or 4 blood samples for the assessment of the immunogenicity of the 3 SP0202 formulations, Prevnar 13 and pediatric vaccines: a sample before injection of PCV (BL0001; 3 mL) at D0 (V01)*, a sample 1 month after PCV Dose 3 (BL0002; 6 mL) at D150 (± 14 days; V04), before PCV Dose 4 (BL0003; 6 mL) at D300-390 (±14 days; V05), and 1 month after PCV Dose 4 (BL0004; 6 mL) at D330-420 (+ 14 days; V06).

Immunogenicity of pneumococcal antigens will be assessed in priority versus concomitants antigens.

Safety

Reactogenicity data will be collected in all participants after each injection. Solicited injection site reactions will be collected for both study and concomitant pediatric vaccines.

All participants will be observed for 30 minutes after vaccination, and clinical site personnel will record any unsolicited systemic AEs occurring during that time as immediate unsolicited systemic AEs in the (electronic) case report book (CRB).

Participants' parents / guardians will record in the DC / eDC information about AEs (solicited and unsolicited), concomitant medications, and any medical visits or hospitalizations.

Solicited injection site and systemic reactions will be collected from D0 to D7 following injection. Unsolicited events will be collected from D0 to D30 following injection. SAEs and AESIs will be collected throughout the study (from D0 until the 6-month follow-up safety phone contact).

* Not applicable from protocol Version 5.0

For both toddlers and infants, anaphylaxis/hypersensitivity, convulsions (including febrile convulsions), hypotonic-hyporesponsive episode, and apnea will be considered as AESIs.

Table 3.3: Table of Study Procedures 1 (Toddlers)

Phase II Trial, 2 Visits, 2 Phone Calls, 1 dose of either one SP0202 formulation or Prevnar 13, along with 1 concomitant dose of Pentacel, 2 Blood Samples, approximately 6-month duration per participant

Visit/Contact	**V01**	**PC1**	**V02**	**PC2** **6-month safety follow-up**
Trial timelines (approximate # of days [D])	D0	D8	D30	D180
Visit intervals		V01 + 8 D	V01 + 30 D	V01 + 6 months
Time windows (days)		+2	+14	+14
Informed consent	X			
Inclusion/exclusion criteria	X			
Collection of demographic data	X			
Medical history	X			
Physical examination and temperature*	X		X	
Randomization/allocation of participant number	X			
Blood sampling (BL), approximately 6 mL†	BL0001		BL0002	
Injection (SP0202 or Prevnar 13)	X			
Injection (pediatric vaccine [Pentacel])	X			
30-Minute observation period	X			
Diary card (DC) / electronic DC (eDC) provided collected	DC1/eDC1		DC1/eDC1	
Memory aid (MA) provided checked			X	X
Telephone contacts		X‡		X**
Injection Site Reactions & Systemic Events Assessment§			X	
Collection of reportable concomitant medications	X		X	
Trial termination record			X	
Collection of SAEs and AESIs	To be reported at any time during the trial			

* Mandatory at injection Visit (before injection). For V02: physical examination and temperature measurement will be performed, if necessary, based on the health status of the participant.

† BL0001 is to be collected prior to any injection (SP0202, Prevnar 13, and Pentacel).

‡ During this call the staff will determine whether the participant experienced any SAE and AESI not yet reported. The site staff will remind participant's parent / guardian to continue using the DC / eDC.

§ Solicited injection site and systemic reactions will be collected for 7 days after injection. Unsolicited AEs will be collected for 30 days after injection.

** During this call the staff will review the MA with the participant's parent / guardian and determine whether the participant experienced any SAE or AESI not yet reported.

Table 3.4: Table of Study Procedures 2 (Infants) (applicable before protocol Version 5.0)

Phase II Trial, 6 Visits, 5 Phone Calls, 4 doses of either one SP0202 formulation or 1 Prevnar 13, concomitant vaccine doses (Pentacel, ENGERIX-B, RotaTeq, M-M-RII, and VARIVAX [as per pediatric schedule]), 4 blood samples, approximately 16 to 19 Months Duration per Participant

Visit (V)	**V01**	**PC1**	**V02**	**PC2**	**V03**	**PC3**	**V04**	**V05***	**PC4**	**V06**	**PC5** **6-month safety follow-up**
Trial timelines (approximate # of days [D])	D0	D8	D60	D68	D120	D128	D150	D300-390	D308	D330-420	D480-570
Visit / Phone contact intervals		V01 + 8	V01 + 60D	V02 + 8D	V02 + 60D	V03 + 8D	V03 + 30D	V03 + 180D*	V05 + 8D	V05 + 30D	V05 + 180D
Time windows (days)		+2	±14	+2	±14	+2	+14	±14	+2	+14	+14
Approximate age of participants (months)	2		4		6		7	12-15		13-16	18 - 21
Informed consent	X										
Inclusion/exclusion criteria	X										
Collection of demographic data/body stature	X										
Medical history	X							X			
Physical examination and temperature†	X		X		X		X	X		X	
IRT contact	X		X		X			X			
Randomization/allocation of participant number	X										
Blood sampling (BL) (approximate volume) ‡	BL0001 (3 mL)						BL0002 (6 mL)	BL0003 (6 mL)		BL0004 (6 mL)	
Injection (SP0202 or Prevnar 13)	X		X		X			X			

Routine pediatric vaccines Pentacel ENGERIX-B§ RotaTeq M-M-R_{II} and Varivax	 X X X -		 X X X -		 X X X -			 - - - X			
30-Minute observation period	X		X		X			X			
Telephone contacts		X**		X**		X**			X**		X††
Diary card (DC) provided collected	 DC1		 DC2 DC1		 DC3 DC2		 DC4 DC3	 DC5 DC4		 DC5	
Memory aid (MA) provided checked										 X	 X
Injection Site Reactions & Systemic Events Assessment	Solicited injection site and systemic reactions: Day 0-7 after each injection Unsolicited adverse events: Day 0-30 after each injection										
Collection of reportable concomitant medications	X		X		X		X	X			
Trial termination record							X			X	
Reporting of SAEs and AESIs	Throughout the trial										

* V05 can take place up until participant reaches 15 months.

† Mandatory at injection Visit (before injection). For other visits: physical examination and temperature measurement will be performed if necessary, based on the health status of the participant.

‡ BL0001 and BL0003 are to be collected prior to injection of study and concomitant vaccines.

§ First dose of hepatitis B vaccine must be given at least 28 days prior to study enrollment (US sites). Infants included in Canada will receive an additional dose of hepatitis B vaccine at V02.

** During the phone calls the staff will determine whether the participant experienced any SAE or AESI not yet reported. The site staff will remind participant's parent / guardian to continue using the DC.

†† During this call the staff will review the MA with the participant's parent / guardian and determine whether the participant experienced any SAE and AESI not yet reported.

Table 3.5: Table of Study Procedures 2 (Infants) (applicable from protocol Version 5.0)

Phase II Trial, 6 Visits, 5 Phone Calls, 4 doses of either one SP0202 formulation or 1 Prevnar 13, concomitant vaccine doses (Pentacel, ENGERIX-B, RotaTeq, M-M-RII, and VARIVAX [as per pediatric schedule]), 3 blood samples, approximately 16 to 19 Months Duration per Participant

Visit (V)	**V01**	**PC1**	**V02**	**PC2**	**V03**	**PC3**	**V04**	**V05***	**PC4**	**V06**	**PC5** **6-month safety follow-up**
Trial timelines (approximate # of days [D])	D0	D8	D60	D68	D120	D128	D150	D300-390	D308	D330-420	D480-570
Visit / Phone contact intervals		V01 + 8	V01 + 60D	V02 + 8D	V02 + 60D	V03 + 8D	V03 + 30D	V03 + 180D*	V05 + 8D	V05 + 30D	V05 + 180D
Time windows (days)		+2	±14	+2	±14	+2	+14	±14	+2	+14	+14
Approximate age of participants (months)	2		4		6		7	12-15		13-16	18 - 21
Informed consent	X										
Inclusion/exclusion criteria	X										
Collection of demographic data/body stature	X										
Medical history	X							X			
Vaccination history	X										
Physical examination and temperature†	X		X		X		X	X		X	
IRT contact	X		X		X			X			
Randomization/allocation of participant number	X										
Blood sampling (BL) (approximate volume) ‡							BL0002 (6 mL)	BL0003 (6 mL)		BL0004 (6 mL)	
Injection (SP0202 or Prevnar 13)	X		X		X			X			

Routine pediatric vaccines Pentacel RotaTeq M-M-R_{II} and Varivax	X X -		X X -		X X -			- - X			
Other pediatric vaccine ENGERIX-B§	X		X		X			-			
30-Minute observation period	X		X		X			X			
Telephone contacts		X**		X**		X**			X**		X††
Diary card (DC) provided collected	DC1		DC2 DC1		DC3 DC2		DC4 DC3	DC5 DC4		DC5	
Memory aid (MA) provided checked										X	X
Injection Site Reactions & Systemic Events Assessment	Solicited injection site and systemic reactions: Day 0-7 after each injection Unsolicited adverse events: Day 0-30 after each injection										
Collection of reportable concomitant medications	X		X		X		X	X			
Trial termination record							X			X	
Reporting of SAEs and AESIs	Throughout the trial										

* V05 can take place up until participant reaches 15 months.

† Mandatory at injection Visit (before injection). For other visits: physical examination and temperature measurement will be performed if necessary, based on the health status of the participant.

‡ BL0003 is to be collected prior to injection of study and concomitant vaccines.

§ Hepatitis B vaccination can be administered concomitantly with Pentacel and PCV doses at V01, V02, and V03. A first dose of hepatitis B vaccine can be given at least 28 days prior to study enrollment.

** During the phone calls the staff will determine whether the participant experienced any SAE or AESI not yet reported. The site staff will remind participant's parent / guardian to continue using the DC.

†† During this call the staff will review the MA with the participant's parent / guardian and determine whether the participant experienced any SAE and AESI not yet reported.

4 Endpoints and Assessment Methods

4.1 Safety Endpoints and Assessment Methods

The primary endpoints for the evaluation of safety are:

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each and any injection of a SP0202 formulation or Prevnar 13, as applicable
- Occurrence of solicited (ie, pre-listed in the participant's DC / eDC and in the CRB) injection site reactions occurring up to D7 after each and any injection of a SP0202 formulation, Prevnar 13, or a concomitant pediatric vaccine, as applicable
- Occurrence of solicited systematic reactions occurring up to D7 after each and any injection of a SP0202 formulation or Prevnar 13, as applicable
- Occurrence of unsolicited (spontaneously reported) AEs up to 30 days after each and any injection of a SP0202 formulation or Prevnar 13, as applicable
- Occurrence of SAEs and AESIs, throughout the study period

4.1.1 Safety Assessment Methods

At each visit, the Investigator or a delegate will perform a clinical or medically driven physical examination and will ask the parent / guardian about any solicited reactions and unsolicited AEs recorded in the DC / eDC, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

4.1.1.1 Immediate Post-vaccination Observation Period

Participants will be kept under observation for 30 minutes after each vaccination to ensure their safety. The post-vaccination observation should be documented in the source document. Any AE that occurs during this period will be noted on the source document and recorded in the CRB, as follows:

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as "yes" and details collected).
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded in the CRB in the same way as any reactions starting on the day of vaccination.
- SAEs will be recorded in the CRB and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in the protocol.

4.1.1.2 Reactogenicity (Solicited Reactions From Day 0 to Day 7 After Each Vaccination)

After each vaccination, participants parents / guardians will be provided with a DC / eDC, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the participants in the diary card on the day of vaccination and for the next 7 days (ie, Day 0 through Day 7) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event (eg, medication)

  The action(s) taken by the parent or guardian to treat and/or manage any **solicited reactions** will be classified in the CRB using the following list (all applicable items should be checked):

  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination

Participants' parents / guardians will be contacted by telephone 8 days after each vaccination to remind them to record all safety information in the DC / eDC.

If the timing of the telephone call should fall on a weekend or a holiday, the call should be made on the next business day. If contact is not made on the designated day, study staff will continue calling until contact is made. Every telephone attempt and its outcome will be documented in the source document.

Table 4.1 and Table 4.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the DC / eDC, and CRB, together with the intensity scales.

Table 4.1: Solicited injection site reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	**Injection site tenderness**	**Injection site erythema**	**Injection site swelling**
Diary card term	Tenderness	Redness	Swelling
Definition	Pain when the injection site is touched or injected limb mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	Grade 1: Minor reaction when injection site is touched Grade 2: Cries or protests when injection site is touched Grade 3 (CRB): Cries when injected limb is mobilized, or the movement of the injected limb is reduced Grade 3 (DC / eDC): Cries when injected limb is moved or the movement of the injected limb is reduced	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

* For the subjective reaction of tenderness, parents /guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

Table 4.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Diary card term	Temperature	Vomiting	Abnormal crying	Drowsiness	Loss of appetite	Irritability
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Vomiting does not include spitting up	Inconsolable crying without a determined reason	Reduced interest in surroundings, or increased sleeping	See intensity scale	An excessive response to stimuli: increased fussiness, whining, and fretfulness despite attempts to comfort the infant and despite caregiver responses that would normally be soothing
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.5°C **or** ≥ 100.4°F to ≤ 101.3°F	Grade 1: 1 episode per 24 hours	Grade 1: < 1 hour	Grade 1: Sleepier than usual or less interested in surroundings	Grade 1: Eating less than normal	Grade 1: Easily consolable
	Grade 2: > 38.5°C to ≤ 39.5°C **or** > 101.3°F to ≤ 103.1°F	Grade 2: 2-5 episodes per 24 hours	Grade 2: 1-3 hours	Grade 2: Not interested in surroundings or did not wake up for a feed / meal	Grade 2: Missed 1 or 2 feeds / meals completely	Grade 2: Requiring increased attention
	Grade 3: > 39.5°C **or** > 103.1°F	Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration	Grade 3: > 3 hours	Grade 3: Sleeping most of the time or difficult to wake up	Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals	Grade 3: Inconsolable

* For all reactions but fever, parents /guardians will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

Parents / guardians are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC / eDC, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is rectal. Pre-vaccination temperature is also systematically collected by the Investigator on the source document. Tympanic thermometers must not be used.

4.1.1.3 Unsolicited Adverse Events

In addition to recording solicited reactions, parents / guardians will be instructed to record any other medical events that may occur during the 30-day period after vaccination for toddlers / between the vaccination and the next visit for infants to be taken as per the study design. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from inclusion (D0) until 6 months after the last vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the "Serious" box on the AE CRF and completing the appropriate Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports). In case a participant experiences febrile convulsion (neurological event associating fever and seizure), the assessment will be performed according to the "Guideline for definition and collection of cases of febrile convulsion", and this event will be considered an SAE.

For each unsolicited AE (whether serious or non-serious), the following information is to be recorded:

- Start and stop dates[a]
- Intensity of the event:

  For measurable unsolicited AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 4.1 and Table 4.2).

  All other unsolicited AEs will be classified according to the following intensity scale:

  - Grade 1

    CRB: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

    DC / eDC: No interference with usual activities.

[a] The stop date of all related AEs will be actively solicited. For other events, the investigator will provide the stop date when it becomes available. AEs for which no stop date was obtained during the course of the study will be considered as ongoing at the end of the study.

- Grade 2

  CRB: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

  DC / eDC: Some interference with usual activities.

- Grade 3

  CRB: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

  DC / eDC: Significant; prevents usual activities.

- Whether the AE was related to the investigational product (for unsolicited systemic AEs)

  The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related"

- Action taken for each AE (eg, medication)

  The action(s) taken by the parent or guardian to treat and/or manage any unsolicited AEs will be classified in the CRB using the following list (all applicable items should be checked):

  - None
  - Medication
  - Health care provider contact
  - Hospitalized
  - Discontinuation of study vaccination

- Whether the AE was serious

  For each SAE, the Investigator will complete all seriousness criteria that apply (outcome, elapsed time, and relationship to study procedures)

- Whether the AE caused study discontinuation

4.1.1.4 Adverse Events of Special Interest

An AESI is an event for which ongoing monitoring and rapid communication by the Investigator to the Sponsor must be done. The following AE will be captured as AESI throughout the study:

- Anaphylaxis defined as per the Brighton collaboration case definition (1)
- Convulsions including febrile convulsions
- Hypotonic-hyporesponsive episode
- Apnea

Because of its medical importance and to ensure expedited communication to the Sponsor, these AESI are to be collected with the same level of information as SAE and reported to the Sponsor according to the procedure described in the protocol. Further instructions on the data collection for this event and the relevant definition will be provided in the Operating Guidelines.

4.1.1.5 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the investigational product administered as either ***not related*** or ***related***, based on the following definitions:

Not related - The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the first vaccination (screening phase, if applicable)

Related - There is a "reasonable possibility" that the AE was caused by the investigational product administered, meaning that there is evidence or arguments to suggest a causal relationship

Note: By convention, all AEs reported at the injection site (whether solicited or unsolicited) and all solicited systemic AEs are considered to be related to the administered product and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

Adverse events likely to be related to the product, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

4.2 Immunogenicity Endpoints and Assessment Methods

A summary of the tests conducted per time point for toddlers and for infants is provided in Table 4.3 and in Table 4.4, respectively. This also includes test carried out for primary endpoints (ie, pneumococcal capsular polysaccharide-electro-chemiluminescent assay [PnPS-ECL]).

The tests are presented by descending order of priority (from highest to lowest).

Table 4.3: Summary of tests per time point in toddlers

Tests	BL0001	BL0002
PnPS-ECL	X	X
MOPA	X	X
Anti-Diphtheria, Tetanus, and Pertussis Antibodies	X	X
Anti-*Haemophilus influenza* type b (Anti-PRP) Antibodies	X	X
Anti-Polio (types 1, 2, and 3) Antibodies	X	X

Table 4.4: Summary of tests per time point in infants

Tests	BL0001*	BL0002	BL0003	BL0004
PnPS-ECL	X	X	X	X
MOPA		X	X	X
Anti-Diphtheria, Tetanus, and Pertussis Antibodies	X	X		
Anti-*Haemophilus influenza* type b (Anti-PRP) Antibodies		X		
Anti-Polio (types 1, 2, and 3) Antibodies		X		
Anti-HB antibodies		X		
Anti-Rotavirus IgA Antibodies	X	X		
Anti-Measles Antibodies				X
Anti-Mumps Antibodies				X
Anti-Rubella Antibodies				X
Anti-Varicella Antibodies				X

4.2.1 Endpoints for Primary Objectives

The primary endpoints for the evaluation of immunogenicity are:

Toddlers (1 dose)

- Serotype specific IgG concentrations for all pneumococcal serotypes included in the SP0202 formulations, as measured by electro-chemiluminescence assay (ECL) at baseline and 30 days post-injection
- Serotype specific IgG concentrations ratios (post-/pre-injection) for each pneumococcal serotype included in the SP0202 formulations, as measured by ECL

Infants (3 doses for primary series + 1 dose as booster)

- Percentage of participants with serotype specific IgG concentration ≥ 0.35 µg/mL for each pneumococcal serotype included in the SP0202 formulations, as measured by ECL at PD3
- Serotype specific IgG concentrations for all pneumococcal serotypes included in the SP0202 formulations, as measured by ECL at baseline*, PD3, before Dose 4, and at PD4
- Serotype specific IgG concentrations ratios (PD3/pre-dose 1* and PD4/pre-dose 4) for each pneumococcal serotype included in the SP0202 formulations, as measured by ECL

* Not applicable from protocol Version 5.0

4.2.2 Endpoints for Secondary Objectives

4.2.2.1 Immunogenicity of SP0202 or Prevnar 13

Toddlers

- Serotype specific OPA titers for all pneumococcal serotypes included in the SP0202 formulations, as determined by multiplex opsonophagocytic assay (MOPA), at baseline, and 30 days post-injection
- Percentage of participants with serotype specific OPA titers ≥ lower limit of quantitation (LLOQ) for each pneumococcal serotype included in the SP0202 formulations, as determined by MOPA, at baseline, and 30 days post-injection
- Serotype specific OPA titers ratio (post-/pre-injection) for each pneumococcal serotype included in the SP0202 formulations, as determined by MOPA

Infants

- Serotype specific OPA titers for all pneumococcal serotypes included in the SP0202 formulations, as determined by MOPA, at PD3, before Dose 4, and at PD4
- Percentage of participants with serotype specific OPA titers ≥ LLOQ for each pneumococcal serotype included in the SP0202 formulations, as determined by MOPA, at PD3, before Dose 4, and at PD4 post-injection
- Serotype specific OPA titers ratio (PD4/pre-dose 4) for each pneumococcal serotype included in the SP0202 formulations, as determined by MOPA

4.2.2.2 Immunogenicity of Concomitant Licensed Vaccines When Co-administered With SP0202 or Prevnar 13

Toddlers

Before vaccination (D0) in all participants:

- Anti-pertussis (pertussis toxoid / toxin [PT], filamentous hemagglutinin [FHA], pertactin [PRN], and fimbriae types 2 and 3[FIM]) Ab concentrations
- Anti-polyribosyl-ribitol phosphate [PRP] Ab concentrations
- Anti-PRP Ab concentrations ≥ 0.15 μg/mL
- Anti- diphtheria toxoid Ab concentrations
- Anti- tetanus toxoid Ab concentrations
- Anti-poliovirus (types 1, 2, and 3) Ab titers

One month post-vaccination (D30) in all participants:

- Anti-PRP Ab concentrations
- Anti-PRP Ab concentrations ≥ 0.15 μg/mL and ≥ 1.0 μg/mL
- Anti-poliovirus (types 1, 2, and 3) Ab titers

- Anti-poliovirus (types 1, 2, and 3) Ab titers ≥ 1:8
- Anti-pertussis (PT, FHA, PRN, and FIM) Ab concentrations
- Anti-pertussis (PT, FHA, PRN, and FIM) vaccine response*

  * Pertussis vaccine response definition:
  - Pre-vaccination < LLOQ, then post-vaccination should be ≥ 4x the LLOQ
  - Pre-vaccination ≥ LLOQ but < 4x the LLOQ, then post-vaccination should achieve a 4-fold rise (post- vaccination/pre-vaccination ≥ 4)
  - Pre-vaccination ≥ 4x the LLOQ, then post-vaccination should achieve a 2-fold response (post-vaccination/pre-vaccination ≥ 2)
- Anti- diphtheria toxoid Ab concentrations
- Anti-diphtheria toxoid Ab concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
- Anti- tetanus toxoid Ab concentrations
- Anti-tetanus toxoid Ab concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL

Infants

Before first vaccination in all participants (D0)*:

- Anti-rotavirus serum immunoglobulin (Ig) Ab concentrations
- Anti-pertussis (PT, FHA, PRN, and FIM) Ab concentrations
- Anti- diphtheria toxoid Ab concentrations
- Anti- tetanus toxoid Ab concentrations

One month after 6 MoA vaccination (D150) in all participants:

- IgG Abs against hepatitis B surface antigen concentration ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Anti-PRP Ab concentrations
- Anti-PRP Ab concentrations ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
- Anti-poliovirus (types 1, 2, and 3) Ab titers
- Anti-rotavirus serum IgA Ab concentrations
- Anti-rotavirus serum IgA Ab concentrations with ≥ 3-fold rise over baseline*
- Anti-pertussis (PT, FHA, PRN, and FIM) Ab concentrations
- Anti- diphtheria toxoid Ab concentrations
- Anti-diphtheria toxoid Ab concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL
- Anti- tetanus toxoid Ab concentrations
- Anti-tetanus toxoid Ab concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL

One month after 12-15 MoA vaccination (D330-D420) in all participants:

- Anti-measles Ab concentrations

*Not applicable from protocol amendment V5.0

- Anti-measles Ab concentrations ≥ 255 mIU/mL
- Anti-mumps Ab concentrations
- Anti-mumps Ab concentrations ≥ 10 mumps Ab U/mL
- Anti-rubella Ab concentrations
- Anti-rubella Ab concentrations ≥ 10 IU/mL
- Anti-varicella Ab concentrations
- Anti-varicella Ab concentrations ≥ 5 glycoprotein enzyme-linked immunosorbent assay (gpELISA) units/mL

4.2.2.3 Immunogenicity Assessment Methods

Pneumococcal capsular polysaccharide - electro-chemiluminescent assay (PnPS-ECL)

[redacted]

This method will be performed on BL0001 and BL0002 collected from toddlers, and on BL0001*, BL0002, BL0003, and BL0004 collected from infants.

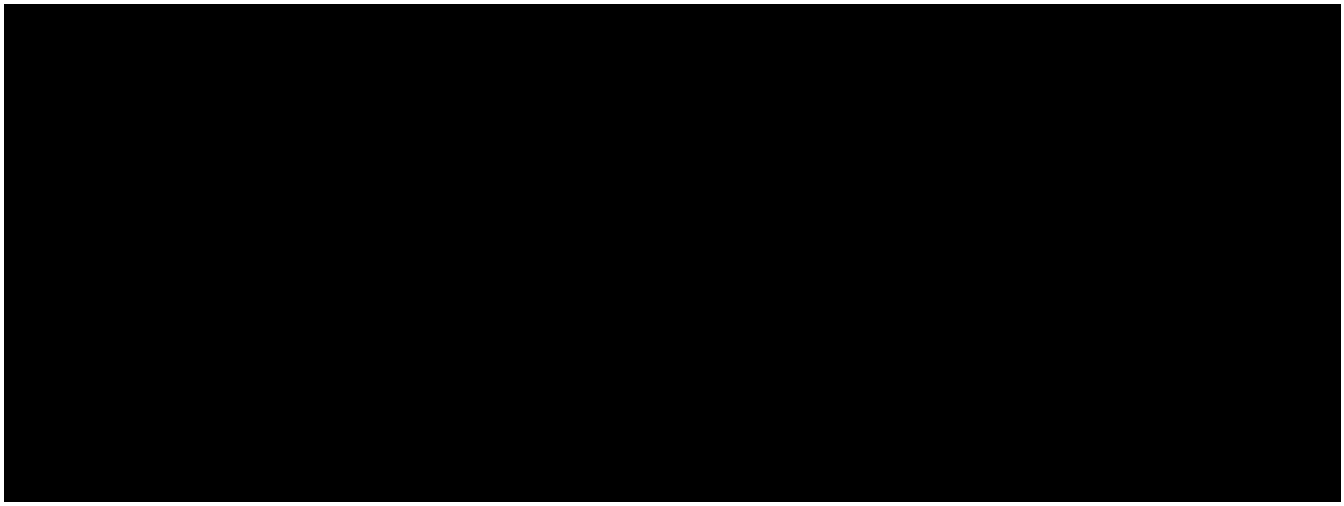
Multiplexed opsonophagocytic killing assay (MOPA)

[redacted]

* Not applicable from protocol Version 5.0

This method will be performed on BL0001 and BL0002 collected from toddlers, and on BL0002, BL0003 and BL0004 collected from a subset of infants.

Anti-Diphtheria, Tetanus, and Pertussis Antibodies



This method will be performed on BL0001* and BL0002 collected from both toddlers and infants.

Anti-Haemophilus influenza type b (Anti-PRP) Antibodies

This method will be performed on BL0001 and BL0002 collected from toddlers and on BL0002 from infants.

* Not applicable from protocol Version 5.0 for infants

Anti-Polio (types 1, 2, and 3) Antibodies

[redacted]

This method will be performed on BL0001 and BL0002 collected from toddlers and on BL0002 from infants.

Anti-Rotavirus IgA Antibodies

[redacted]

This method will be performed on BL0001* and BL0002 collected from infants.

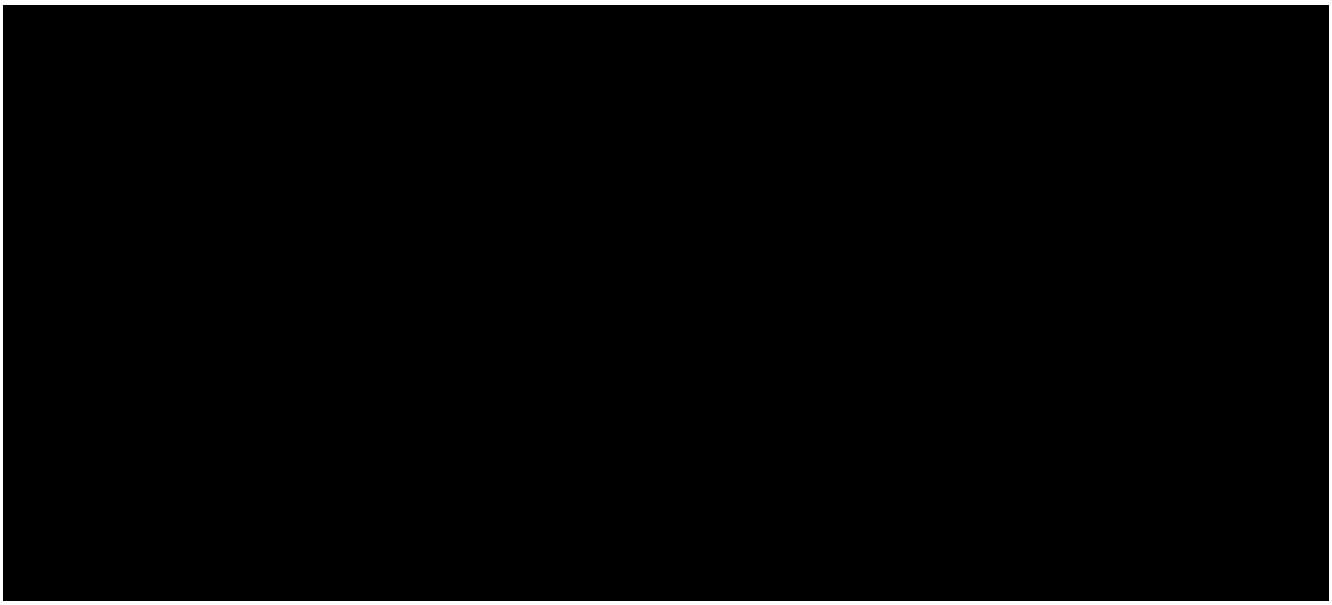
Anti-Hepatitis B Antibodies

[redacted]

* Not applicable from protocol Version 5.0

This method will be performed on BL0002 collected from infants.

Anti-Measles Antibodies

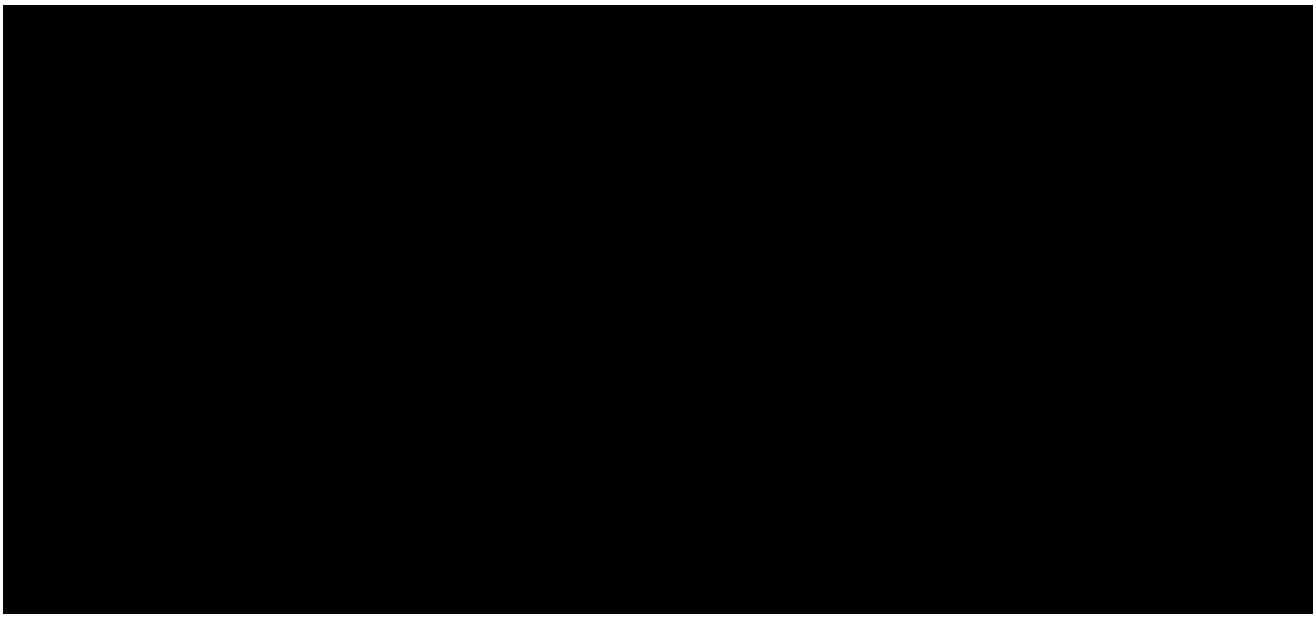


This method will be performed on BL0004 collected from infants.

Anti-Mumps Antibodies

This method will be performed on BL0004 collected from infants.

Anti-Rubella Antibodies



This method will be performed on BL0004 collected from infants.

Anti-Varicella Antibodies

This method will be performed on BL0004 collected from infants.

4.3 Derived Endpoints: Calculation Methods

4.3.1 Safety

4.3.1.1 Solicited Reactions

4.3.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

For the derivation of daily intensities, the following sequential steps will be applied:

1) Solicited reactions (except Fever/Pyrexia) with an investigator presence recorded as "No" and with all daily records missing (Unknown) then all daily intensities will be derived as None (applicable only for Stage II using DC).
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3.

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.3.1.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.3.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.3.1.1.3 Presence (Occurrence)

Presence is derived from the maximum overall intensity over the time period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing or Unknown: Missing presence

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

The time period is displayed as D0-D3, D4-D7, D8 and later.

4.3.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.3.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (ie, reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first presence.

Time of onset period is displayed as, D0-D3, D4-D7.

4.3.1.1.5 Number of Days of Presence (Occurrence)

Number of days of presence over the period considered is derived from the daily intensities computed as described in Section 4.3.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

4.3.1.1.6 Number of Days of Presence (Occurrence) During the Solicited Period

Number of days of presence over the period considered is derived from the daily intensities computed as described in Section 4.3.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

4.3.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.3.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1.

Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.

Missing: all other conditions (in this case, it won't be included in the denominator of the ongoing analysis in the safety tables).

4.3.1.2 Unsolicited AEs

4.3.1.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event.

Grade 0 events should be included in separate listings.

4.3.1.2.2 Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule than the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Intensity for the other unsolicited AEs will correspond to the value reported in the CRF.

The maximum intensity corresponds to the highest intensity for a unique term.

4.3.1.2.3 Last Vaccination

Last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the unsolicited AE form and is calculated as follows:

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date should be used to determine the last vaccination before the unsolicited AE
- If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, should be used to determine the last vaccination before the unsolicited AE

4.3.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of last vaccination as described in Section 4.3.1.2.3.

Time of Onset = start date of the unsolicited AE - date of last vaccination before the unsolicitedAE

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited AEs will be analyzed "Within 30 days" after each vaccination, which corresponds to AEs with a time of onset between 0 and 30 days or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number in "Appeared after visit" or similar field, so will be included in these tables.

Time of onset period is displayed as D0-D3, D4-D7, D8-D14, D15 or later, and Missing.

Note: Unsolicited AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis but will be listed separately.

4.3.1.2.5 Duration

Duration is derived from the start and end dates of the unsolicited AE:

- Duration = End date of unsolicited AE - start date of unsolicited AE + 1.

The duration should be considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

4.3.1.2.6 SAEs

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF.

SAEs will be analyzed throughout the study using at least the following periods:

- Within 30 days after (each) injection
- During post-Dose i period (ie, between injection i and injection i+1 [for each injection except for the last one of the primary series], and within 30 days after the last injection of the primary series for Infant)
- During the 6-month follow-up period (ie, from 31 days after the last injection until the last participant contact)
- During the study (ie, all SAEs occurred during the study)

4.3.1.2.7 AESIs

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF.

AESIs will be analyzed throughout the study using the following periods:

- Within 30 days after (each) injection
- During post-Dose i period (ie, between injection i and injection i+1 [for each injection except for the last one of the primary series], and within 30 days after the last injection of the primary series for Infant)
- During the 6-month follow-up period (ie, from 31 days after the last injection until the last participant contact)
- During the study (ie, all AESIs occurred during the study)

4.3.1.3 Other Safety Endpoints

4.3.1.3.1 Injection Site Necrosis and Exfoliative Dermatitis

For the purpose of the Early Safety Data Review (ESDR) conducted by the SMT/DMC, a specific focus will be done on the following events: Injection site necrosis and Exfoliative dermatitis. These events will be identified also in the main statistical analysis among reported unsolicited AE using the following MedDRA preferred terms:

	MedDRA 23.1 preferred terms
Injection site necrosis	Injection site necrosis, Vaccination site necrosis, Application site necrosis, Extremity necrosis, Necrosis, Soft tissue necrosis, Administration site necrosis, Skin necrosis
Exfoliative dermatitis	Dermatitis exfoliative, Dermatitis exfoliative generalised, Exfoliative rash, Injection site rash, Vaccination site rash, Application site rash, Injection site dermatitis, Vaccination site dermatitis, Application site dermatitis, Administration site dermatitis

4.3.1.3.2 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.3.1.3.3 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.3.1.3.4 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.3.1.3.5 Causal Relationship

This information will be summarized as collected in the field "Relationship to Investigational Product". Missing causal relationship will be handled as described in Section 5.3.1.2. Relationship to non-investigational product (ie, Concomitant vaccines) is collected for the Unsolicited Injection Sites Reactions and be presented in summary tables and in the listings. Relationship to study procedure for SAE is only presented in the listings.

4.3.1.3.6 AEs Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.

In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Study" form question "What was the participant's status?" has "Adverse Event" checked.
- Safety overview table: A participant who has either on the "Completion at End of Study" form, question "What was the participant's status?" has "Adverse Event" checked or lists a solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.
- SOC/PT table: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

4.3.2 Immunogenicity

4.3.2.1 Computed Values for Analysis

In order to appropriately manage extreme values ('< LLOQ' and '≥ ULOQ'), lower limit of quantitation and upper limit of quantitation, respectively, for analysis purposes of Geometric Mean Titer (GMTs) / Geometric Mean Concentration (GMCs) and percentage above cut-offs, the following computational rules will be applied to the values provided in the clinical database:

- If a value is '<LLOQ', then the computed value is LLOQ/2
- If a value is '≥ ULOQ' or '>ULOQ', then the computed value is ULOQ
- otherwise, the computed value is the value

4.3.2.2 Thresholds

Generally, if the computed value is ≥ x, then the derived indicator will be "Yes" for that test, otherwise indicator will be "No". Note: If the computed value is missing, indicator will be missing. The thresholds are summarized in the tables below:

Table 4.5: Immunogenicity Thresholds of interest for Stage 1/ Toddlers

Endpoints	**Baseline (V01)**	**30 days post-injection (V02)**
Pneumococcal serotype specific binding IgG	≥ 0.35 µg/mL	≥ 0.35 µg/mL
Pneumococcal serotype specific functional Ab (OPA)	≥ LLOQ (1/dil)	≥ LLOQ (1/dil)
Anti-diphtheria and anti-tetanus Ab	≥ 0.1 IU/mL, ≥ 1.0 IU/mL	≥ 0.1 IU/mL, ≥ 1.0 IU/mL
Anti-poliovirus 1, 2, and 3 Ab	≥ 8 (1/dil)	≥ 8 (1/dil)
Anti-PRP Ab	≥ 0.15 µg/mL ≥ 1.0 µg/mL	≥ 0.15 µg/mL ≥ 1.0 µg/mL

Table 4.6: Immunogenicity Thresholds of interest for Stage 2/ Infants

Endpoints	**Baseline (V01)***	**30 days post-Dose 3 (V04)**	**Before Dose 4 (V05)**	**30 days post-Dose 4 (V06)**
Pneumococcal serotype specific binding IgG	≥ 0.35 µg/mL	≥ 0.35 µg/mL	≥ 0.35 µg/mL	≥ 0.35 µg/mL
Pneumococcal serotype specific functional Ab (OPA)		≥ LLOQ (1/dil)	≥ LLOQ (1/dil)	≥ LLOQ (1/dil)
Anti-diphtheria and anti- tetanus Ab	≥ 0.01 IU/mL, ≥ 0.1 IU/ mL, ≥ 1.0 IU/mL	≥ 0.01 IU/mL, ≥ 0.1 IU/ mL, ≥ 1.0 IU/mL		
Anti-poliovirus 1, 2, and 3 Ab	-	≥ 8 (1/dil)		
Anti-PRP Ab	-	≥ 0.15 µg/mL ≥ 1.0 µg/mL		
Anti-hepatitis B Ab	-	≥ 10 mIU/mL ≥ 100 mIU/mL		
Anti-measles Ab			-	≥ 255 mIU/mL
Anti-mumps Ab			-	≥ 10 mumps Ab U/mL
Anti-rubella Ab			-	≥ 10 IU/mL
Anti-varicella Ab			-	≥ 5 glycoprotein units/mL

4.3.2.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values. The following algorithm will be used to minimize the numerator and maximize the denominator.

• If the baseline computed value is < LLOQ and the post-baseline computed value is < LLOQ then the fold-rise is 1

* Not applicable from protocol version 5.0

• If the baseline computed value is ≥ LLOQ and the post-baseline computed value is ≥ LLOQ then the fold-rise is post-baseline computed value / baseline computed value

• If the baseline computed value is ≥ LLOQ and the post-baseline computed value is < LLOQ then the fold-rise is (LLOQ/2) / baseline computed value

• If the baseline computed value is < LLOQ and the post-baseline computed value is ≥ LLOQ then the fold-rise is post-baseline computed value /LLOQ

If the computed value is ≥ X-fold rises, then the derived ≥ X fold rises indicator will be

“Yes” for that test, otherwise ≥ X-fold rises will be "No".

Note: If baseline or post-baseline is missing, then fold-rise is missing.

4.3.2.4 Seroconversion

Not applicable.

4.3.2.5 Vaccine Response

Vaccine Response is to be derived for each anti-pertussis antigens (PT, FHA, PRN, and FIM) Ab concentrations as follow:

- Pre-vaccination < LLOQ, then post-vaccination should be ≥ 4x the LLOQ
- Pre-vaccination >= LLOQ but < 4x the LLOQ, then post-vaccination should achieve a 4-fold rise (post- vaccination/pre-vaccination ≥ 4)
- Pre-vaccination >= 4x the LLOQ, then post-vaccination should achieve a 2-fold response (post-vaccination/pre-vaccination ≥ 2)

Pre vaccination concentrations < LLOQ will be converted to LLOQ for purposes of calculating this vaccine response. If the pre-vaccination concentration is missing or No Result (NR) or if the post-vaccination concentration is missing or NR, then the vaccine response is missing.

4.3.3 Efficacy

Not applicable.

4.3.4 Derived Other Variables

4.3.4.1 Age for Demographics

Calendar age will be use in the analysis expressed in Months for Stage I participants and Days/Weeks for Stage II participants.

4.3.4.2 Duration of the Study

The duration will be computed in days as follows: Latest period date - earliest period date + 1.

For Infants, primary series duration will be calculated as follows:

[Date of latest Visit 04 - date of earliest Visit 01] + 1

And booster phase duration will be calculated as follows:

[Date of latest Visit 06 - date of earliest Visit 05] + 1

4.3.4.3 Participant Duration

The duration of a participant participation in the study will be computed as follows:

Maximum (Visit dates, Termination date, Follow-up date, Last contact date) - V01 date + 1.

For infant's primary series, the duration of participant participation will be computed as follows:

[Maximum (Visit dates (Visit 01 up to Visit 04), Termination date (if prematurely withdrawn before the 3rd vaccination), Last contact date (if prematurely withdrawn after the 3rd vaccination and before the 4th vaccination)) - Visit 01 date] + 1.

For the booster phase, the duration of participant participation will be computed as follows:

[Maximum (Visit dates (Visit 05 up to Visit 06), Termination date (if prematurely withdrawn post 4th vaccination), Last contact date)) - Visit 05 date] + 1.

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 software or later.

The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of participants. Percentage of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs) of participants. Unsolicited: Number and percentage (95% CIs) of participants, and number of events.
Immunogenicity results	**Categorical data (seroprotection, cutoff, thresholds)**	Number and percentage (95% CIs) of participants.
	Continuous data (titer / data)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC). Boxplots and Forest plots.

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (2)), ie, using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that Log10 transformation of the titers / concentrations follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

CIs of the difference of proportions between 2 groups will be computed using the Wilson Score method without continuity correction. CIs of ratio of GMTs / GMCs between 2 groups will be computed from the difference in means of log10 transformed titers/concentrations between 2 groups with normal approximation.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objectives

No hypotheses will be tested.

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

5.1.1.1 Hypotheses

5.1.1.2 Statistical Methods

Disposition, demographics, medical history and concomitant medications data will be summarized using counts and percentages.

Safety

Safety results will be analyzed for participants in the safety analysis set (SafAS) who at least received one of the vaccines. The main parameters will be described with 95% CI. At least the following parameters will be presented by group after each/any vaccination(s) as applicable:

- Immediate unsolicited systemic AEs
- Solicited injection site reactions and solicited systemic reactions occurring within 7 days after the day of injection (D0 to D7) according to occurrence (presence), time of onset, intensity (Grade 1, Grade 2, or Grade 3), number of days of occurrence (presence) and action taken
- Unsolicited AEs occurring within 30 days after injection by system organ class (SOC) and PT, relationship, intensity, time of onset, and duration
- All SAEs that occur throughout the study by SOC and PT, relationship and seriousness criteria
- All AESIs that occur throughout the study by SOC and PT and relationship

Immunogenicity - Stage I toddlers

The point estimates and their 95% CI of the following parameters will be presented for each group before and 1-month post-vaccination for each pneumococcal serotype specific IgG concentrations:

- GM of serotype specific IgG concentrations
- GM of IgG concentrations ratio (post- / pre-vaccination)

In addition, the difference between any SP0202 group (Group 1 to 3) and the Prevnar 13 group (Group 4) will be presented in terms of:

- GM ratio of serotype specific IgG concentrations between groups (SP0202/Prevnar 13) and 95% CI at 1-month post-vaccination

Immunogenicity - Stage II infants

The point estimates and their 95% CI of the following parameters will be presented for each group for each pneumococcal serotype specific IgG concentrations when applicable:

- Percentage of participants with a PD3 and PD4 serotype specific IgG concentrations ≥ 0.35 µg/mL
- GM of serotype specific IgG concentrations / titers (pre-dose 1* as applicable, PD3, pre-dose 4, PD4)

- GM of serotype specific IgG concentrations / titers ratio (PD3/pre-dose 1* as applicable, PD4/pre-dose 4)

In addition, difference between any SP0202 group (Group 5 to 7) and the Prevnar 13 group (Group 8) and between SP0202 groups will be presented in terms of:

- Differences of percentages of participants with serotype specific IgG concentration ≥ 0.35 µg/mL and 95% CI at PD3
- GM ratio of serotype specific IgG concentrations between groups and 95% CI at PD3 and PD4

Several graphical representations will be used such as: RCDCs of individual concentrations, Boxplots of the $\log_{10}$ concentrations and Forest plots of GMCs for all serotypes.

*Pre-dose 1 BL is done only for participants enrolled before protocol amendment V5.0

Table 5.2: Summary of statistical analyses for immunogenicity analysis of primary endpoints

Endpoint	Visit and Group	Description
Serotype specific pneumococcal IgG concentration for each of the 21 serotypes	V01 and V02 - Toddlers V01*, V04, V05 and V06 - Infants	IgG GMC and 95% CI, corresponding Forest Plot
	V02/V01 - Toddlers V04/V01*, V06/V05 - Infants	IgG GM ratio (post/pre) and 95%CI
	V01 and V02 - Toddlers V01*, V04, V05 and V06 - Infants	Proportion of participants with concentration ≥ 0.35µg/mL and 95% CI, corresponding Forest Plot
	V02 - Toddlers V04 and V06 - Infants	IgG GMC ratio and 95% CI between any SP0202 group and Prevnar 13 (ie, Group 1/Group 4, Group 2/Group 4, Group 3/ Group 4; Group 5/Group 8, Group 6/Group 8, Group 7/Group 8) and corresponding Forest Plot
	V04 and V06 - Infants	IgG GMC ratio and 95% CI between SP0202 groups (ie, Group 6/Group 5, Group 7/Group 5 and Group 7/Group 6) and corresponding Forest Plot
	V04 - Infants	Difference of proportion of participants with concentration ≥ 0.35 and 95% CI between any SP0202 group and Prevnar 13 (ie, Group 5 - Group 8, Group 6 - Group 8 and Group 7 - Group 8) and between SP0202 groups (ie, Group 6 - Group 5, Group 7 - Group 5 and Group 7 - Group 6), and corresponding Forest Plot
	V01 and V02 - Toddlers V04, V05 and V06 - Infants	IgG concentration RCDC
	V01 and V02 - Toddlers V04, V05 and V06 - Infants	IgG concentration boxplot

*Pre-dose 1 BL is done only for participants enrolled before protocol amendment V5.0

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Hypotheses

5.1.2.2 Statistical Methods

No hypotheses were tested. For descriptive purposes, the statistics presented on Table 5.1 will be produced.

5.1.2.2.1 Stage I toddlers

Immunogenicity of SP0202 or Prevnar 13

The point estimates and their 95% CI of the following parameters will be presented for each group before and 1-month post-vaccination for pneumococcal serotype specific OPA titers:

- GM of serotype specific titers, GM of titers ratio (post- / pre-vaccination)
- Percentage of participants with a serotype specific titer above or equal to LLOQ

In addition, the difference between any SP0202 group (Group 1 to 3) and the Prevnar 13 group (Group 4) will be presented in terms of:

- GM ratio between groups (SP0202/Prevnar 13) and 95% CI at 1-month post-vaccination

Several graphical representations will be used such as: RCDCs of individual concentrations and Forest plots of GMTs for all serotypes.

Immunogenicity of concomitant vaccine

The point estimates and their 95% CI of the following parameters will be presented for each group before and 1-month post-vaccination for Pentacel antigens:

- GM of concentrations / titers for all antigens
- Percentage of participants with concentration / titer above the predefined threshold, including those defining seroprotection
- Vaccine response rate for pertussis (PT, FHA, PRN, and FIM) antigens

RCDCs of individual concentrations / titers will be presented for all serotypes / antigens.

5.1.2.2.2 Stage II infants

Immunogenicity of SP0202 or Prevnar 13

The point estimates and their 95% CI of the following parameters will be presented for each group in the OPA subset and for each pneumococcal serotype specific OPA titers:

- Percentage of participants with a PD3 and PD4 serotype specific titer above or equal to LLOQ
- GM of serotype specific titers (PD3, pre-dose 4, PD4)
- GM of serotype specific titers ratio (PD4/pre-dose 4)

In addition, the difference between any SP0202 group (Group 5 to 7) and the Prevnar 13 group (Group 8) and between SP0202 groups will be presented in terms of:

- GM ratio between groups and 95% CI at PD3 and PD4

Several graphical representations will be used such as: RCDCs of individual concentrations and Forest plots of GMCs for all serotypes.

Immunogenicity of concomitant vaccines:

The point estimates and their 95% CI of the following parameters will be presented for each group for concomitant vaccines (Pentacel, ENGERIX-B, RotaTeq, M-M-RII, and VARIVAX) antigens:

- GM of concentrations / titers for all antigens (at pre-Dose 1* for RotaTeq, Diphteria, Tetanus and Pertussis antigens; at PD3 for ENGERIX-B†, RotaTeq, and Pentacel; at PD4 for M-M-RII and VARIVAX)
- Percentage of participants with concentrations / titers above predefined thresholds, including those defining seroprotection (at PD3 and PD4 as applicable)

RCDCs of individual concentrations / titers will be presented for all serotypes / antigens.

As Engerix-B vaccine was not mandatory from protocol amendment V5.0 and therefore number of doses administered will differ according to countries, the level of antibodies measured will be analyzed according to number of doses of Hepatitis-B vaccine received before and during the study.

* Pre-dose 1 BL is done only for participants enrolled before protocol amendment V5.0

Table 5.3: Summary of Statistical analyses for immunogenicity analysis of secondary endpoints

Endpoint	Visit and Group	Description
Serotype specific pneumococcal OPA titer for each of the 21 serotypes	V01 and V02 - Toddlers V04, V05 and V06 - Infants OPA subset	OPA GMT and 95% CI, corresponding Forest Plot
	V02/V01 - Toddlers V06/V05 - Infants OPA subset	OPA GM ratio (post/pre) and 95% CI
	V01 and V02 - Toddlers V04, V05 and V06 - Infants OPA subset	Proportion of participants with titer ≥ LLOQ and 95% CI
	V02 - Toddlers V04 and V06 - Infants OPA subset	OPA GMT ratio and 95% CI between any SP0202 group and Prevnar 13 (ie, Group 1/Group 4, Group 2/Group 4, Group 3/ Group 4; Group 5/Group 8, Group 6/Group 8, Group 7/Group 8) and corresponding Forest Plot
	V04 and V06 - Infants OPA subset	OPA GMT ratio and 95% CI between SP0202 groups (ie, Group 6/Group 5, Group 7/Group 5 and Group 7/Group

* Not applicable from protocol Version 5.0

† Immunogenicity to ENGERIX-B will be presented according to the number of doses received

		6), and corresponding Forest Plot
	V01 and V02 - Toddlers V04, V05 and V06 - Infants OPA subset	OPA titer RCDC
Anti-tetanus and anti-diphtheria	V01 and V02 - Toddlers V01* and V04 - Infants	GMC and 95% CI
		RCDC
		Proportion of participants with concentration ≥ 0.10 IU/mL and 95% CI
		Proportion of participants with concentration ≥ 1.0 IU/mL and 95% CI
	V01* and V04 - Infants	Proportion of participants with concentration ≥ 0.01 IU/mL and 95% CI
Anti-PT, anti-FHA, anti-PRN and anti-FIM	V01 and V02 - Toddlers V01* and V04 - Infants	GMC and 95% CI
		RCDC
	V02/V01 - Toddlers	Proportion of participants with pertussis vaccine response from pre to post vaccination and 95% CI
Anti-PRP	V01 and V02 - Toddlers V04 - Infants	GMC and 95% CI
		Proportion of participants with concentration ≥ 0.15 µg/mL and 95% CI
		Proportion of participants with concentration ≥ 1.0 µg/mL and 95% CI
		RCDC
Anti-Hepatitis B	V04 - Infants	GMC and 95% CI
		RCDC
		Proportion of participants with concentration ≥ 10 IU/mL and 95% CI
		Proportion of participants with concentration ≥ 100 IU/mL and 95% CI
Anti-Rotavirus	V01*, V04 - Infants	GMC and 95% CI
		RCDC
Anti-measles	V06 - Infants	GMC and 95% CI
		RCDC
		Proportion of participants with concentration ≥ 255 mIU/mL and 95% CI
Anti-mumps	V06 - Infants	GMC and 95% CI
		RCDC
		Proportion of participants with concentration ≥ 10 mumps Ab U/mL and 95% CI

Anti-rubella	V06 - Infants	GMC and 95% CI
		RCDC
		Proportion of participants with concentration ≥ 10 IU/mL and 95% CI
Anti-varicella	V06 - Infants	GMC and 95% CI
		RCDC
		Proportion of participants with concentration ≥ 5 glycoprotein units/mL and 95% CI

* Not applicable from protocol Version 5.0

5.1.3 Complementary analyses

COVID-19

Impact of COVID-19 pandemic on study conduct and disposition of participants impacted by COVID-19 pandemic situation will be summarized in tables on all participants and listed in Appendix 16 of the CSR.

If more than 20% for Stage I (Toddlers)/10% for Stage II (Infants) of randomized participants are impacted by COVID-19, and still evaluable for immunogenicity/safety at primary timepoints, additional analyses in impacted/non-impacted participants will be done on main immunogenicity and safety endpoints.

Subgroup Immunogenicity analyses

For Infant participants, exploratory analyses will be done according to Gender (two categories: Male, Female) and Race (two categories: the modality(ies) the most represented versus the pool of the other modalities) on the main parameters:

- Percentage of participants with a PD3 serotype specific IgG concentrations ≥ 0.35 µg/mL
- GM of serotype specific IgG concentrations (PD3, pre-dose 4, PD4)
- GM of serotype specific ratio concentrations (PD4/pre-dose 4)

Correlation heatmap Immunogenicity analyses

Correlation heatmaps will be plotted for both serotype specific IgG concentrations and serotype specific OPA titers at post-vaccination for Stage I (Toddlers) and at post-dose 3 and post-dose 4 for Stage II (Infants) using the Spearman's correlation matrix across serotypes. One figure for each group separately will be plotted, and one figure pooling the three SP0202 groups will be plotted as well.

Stage 2 participants with blood sample at V01

Participants enrolled prior to implementation of protocol Version 5.0 were to have blood sample at V01 (pre-dose 1 BL).

Main immunogenicity analysis after primary series on pneumococcal serotype specific IgG concentrations, will be performed on participants with blood sample at V01.

The subgroup and correlation analyses will be conducted in the FAS (FAS1, FAS2 or FAS3) and provided in Appendix 15 of the CSR.

5.2 Analysis Sets

Three analysis sets will be used: The Per-Protocol Analysis Set, the Full Analysis Set, and the Safety Analysis Set.

5.2.1 Per-Protocol Analysis Set

The per-protocol analysis set (PPAS) is a subset of the FAS. Three PPAS will be defined: one for Toddlers (PPAS1), one for Infants at Primary series (PPAS2) and one for Infants at Booster (PPAS3).

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS1-Toddlers:

- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Participant did not receive vaccine
- Participant received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Participant did not provide the post-dose serology sample V02 in the proper time window or a post-dose serology sample was not drawn
- Participant received a protocol-prohibited medication or vaccine (identified among category 2 and 3 of concomitant medications)

In addition to the reasons listed above, participants will also be excluded from the PPAS1 if their V02 serology sample did not produce a valid serotype specific IgG test result (ie, results for all serotypes are missing).

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS2 Infants Primary series:

- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria*
- Participant did not complete the vaccination schedule up to V03
- Participant received a vaccine schedule other than the one that he / she was randomized to receive

* The inclusion criteria number 8 “Infants who received the first dose of hepatitis B vaccine at least 28 days before the first study visit (applicable only to infants from the US)” was applicable only before protocol amendment V5.0

- Preparation and / or administration of vaccine was not done as per-protocol
- Participant did not receive vaccine in the proper time window
- Participant did not provide the post-dose serology sample V04 in the proper time window or a post-dose serology sample was not drawn
- Participant received a protocol-prohibited medication or vaccine (identified among category 2 and 3 of concomitant medications) up to V04

In addition to the reasons listed above, participants will also be excluded from the PPAS2 if their V04 serology sample did not produce a valid serotype specific IgG test result (ie, results for all serotypes are missing).

The participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS3-Infants Booster dose:

- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria*
- Participant did not complete the vaccination schedule up to V05
- Participant received a schedule other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Participant did not receive booster vaccine in the proper time window, ie, at 12-15 months of age and at least at V03 +180 days (±14)
- Participant did not provide the post-dose serology sample V06 in the proper time window or a post-dose serology sample was not drawn
- Participant received a protocol-prohibited medication or vaccine (identified among category 2 and 3 of concomitant medications) during the booster phase

In addition to the reasons listed above, participants will also be excluded from the PPAS3 if their V06 serology sample did not produce a valid serotype specific IgG test result (ie, results for all serotypes are missing).

In the event of a local or national immunization program with a pandemic influenza vaccine or a COVID-19 vaccine, participants who receive pandemic influenza vaccine or COVID-19 vaccine at any time during the study will not be withdrawn from the study.

5.2.2 Full Analysis Set

Three FAS will be defined: one for Toddlers (FAS1), one for Infants at Primary series (ie, after 3 doses) (FAS2) and one for Infants at Booster (FAS3):

- The full analysis set (FAS)1 - Toddlers: is defined as the subset of randomized participants to Groups 1 to 4 who received at least 1 dose of the study vaccine and had a valid post-

* The inclusion criteria number 8 “Infants who received the first dose of hepatitis B vaccine at least 28 days before the first study visit (applicable only to infants from the US)” was applicable only before protocol amendment V5.0

vaccination blood sample result (serotype specific IgG concentration or serotype specific OPA titer for at least 1 serotype, or titer/concentration for at least one antigen on the concomitant vaccines)

- The FAS2 - Infants: is defined as the subset of randomized participants to Groups 5 to 8 who received at least 1 dose of the study vaccine in the primary series and had a valid post-primary series vaccination blood sample result (serotype specific IgG concentration or serotype specific OPA titer for at least 1 serotype, or titer/concentration for at least one antigen on the concomitant vaccines)
- The FAS3 - Infants: is defined as the subset of randomized participants to Groups 5 to 8 who received at least 1 dose of the study vaccine at the time of booster and had a valid post-booster vaccination blood sample result (serotype specific IgG concentration or serotype specific OPA titer for at least 1 serotype, or titer/concentration for at least one antigen on the concomitant vaccines)

5.2.3 Safety Analysis Set

The safety analysis set (SafAS) is defined as those participants who have received at least one dose of the study vaccines and have any safety data available. All participants will have their safety analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the 1st dose.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

5.2.4 Other Analysis Set

Randomized participants:
A randomized participant is a participant for whom an injection group has been allocated.

5.2.5 Populations Used in Analyses

Disposition of participants will be described in ‘Randomized Participants’.

The primary and secondary immunogenicity analyses will be performed first on the PPAS (PPAS1, PPAS2, PPAS3) analysis set and then in FAS (FAS1, FAS2, and FAS3). In the FAS, participants will be analyzed by the vaccine group to which they were randomized.

The safety analysis will be performed on the SafAS. Participants will be analyzed according to the vaccine they actually received.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

Generally, no replacement will be done. However, imputations may be done for a limited number of scenarios, some of which are described in this section. In all participant listings, partial and missing data will be clearly indicated as missing.

5.3.1.1 Immediate

For unsolicited systemic AEs, a missing response to the "Immediate" field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

5.3.1.2 Causal relationship

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions. For unsolicited systemic AE, missing relationship will be considered as related to investigational product at the time of analysis. The missing relationship to study procedures for SAEs will not be imputed.

5.3.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.3.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

5.3.1.4 Start Date and Stop Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the visit number collected in "Appeared after visit" or similar field. If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

5.3.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

Missing data will not be imputed. No test or search for outliers will be performed.

For the calculation of GMTs / GMCs and percentage above cut-offs, any pre-vaccination or post-vaccination value reported as '< lower limit of quantification (LLOQ)' will be converted to a value of 0.5 LLOQ.

For the calculation of fold increase and GMTR / GMCR, any pre-vaccination value reported as '< LLOQ' will be converted to LLOQ, and any post-vaccination value reported as '< LLOQ' will be converted to a titer of 0.5 LLOQ when only either the numerator or the denominator is '< LLOQ'. If both numerator and denominator are '< LLOQ', then both will be converted in the same way so that the increase is defined as 1.

Any value reported as '> ULOQ (upper limit of quantitation) or ≥ULOQ' will be converted to ULOQ.

5.3.3 Efficacy

Not applicable

5.4 Interim / Preliminary Analysis

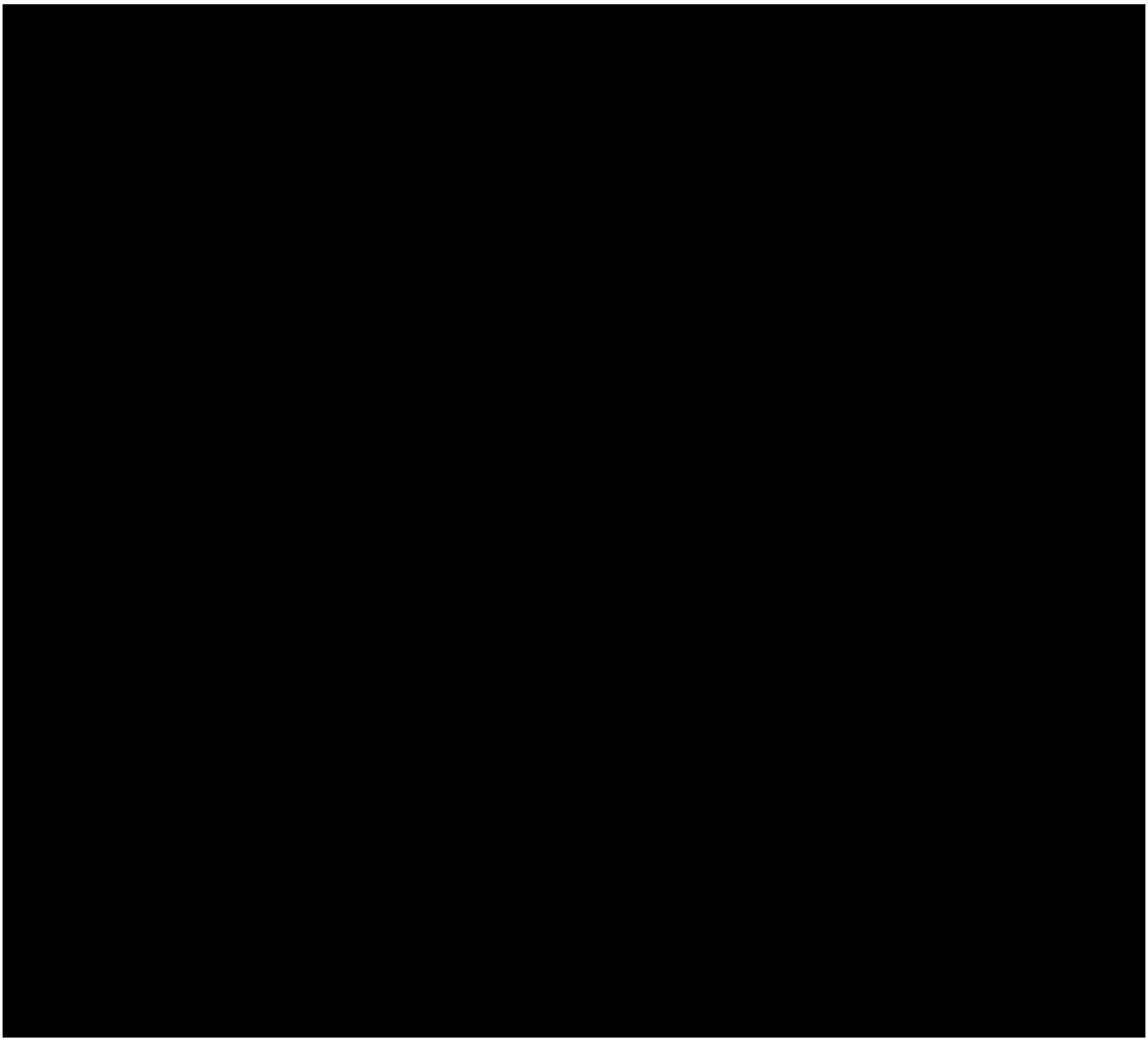
Early Safety Data Review

As part of the ESDR, the SMT and the DMC will assess the D0-D30 safety data of at least [redacted]% of participants from Stage I (Toddlers) to determine whether enrollment of Stage II (Infants) can start as planned (once Stage I enrolment is completed). Additional DMC analyses may be conducted on unblinded Stage I/Stage II participants to monitor the safety during the conduct of the trial. Such analyses are described in the DMC charter. No statistical adjustment is necessary for these descriptive analyses because no hypotheses will be tested.

The sponsor SMT review will be blinded whereas the DMC review will be performed in an unblinded manner. The DMC reports will be provided by an independent statistician to Sanofi Pasteur and will not be communicated to the Sponsor until the end of the trial neither to investigational sites.

Statistical analyses

[redacted]



- If needed, a final analysis will be conducted once the 6-month safety data post-Dose 4 of Stage II participants has been collected and the final database lock has occurred.

5.5 Determination of Sample Size and Power Calculation

The number of participants is designed to provide immunogenicity and safety data on the 3 SP0202 formulations and on Prevnar 13 after each and any injection, as applicable in toddlers, and infants.

The sample size was set at 35 participants per group (140 toddlers) in Stage I and 175 participants per group (700 infants) in Stage II. Assuming a drop-out rate of approximatively 10% in the toddlers, 20% (PD3) and 30% (PD4) in infants, a total of 31, 140, and 122 evaluable participants per group is anticipated for toddlers, infants at PD3, and infants at PD4, respectively.

5.6 Data Review for Statistical Purposes

No blind review of data was performed.

5.7 Changes in the Conduct of the Trial or Planned Analyses

The endpoint "Anti-poliovirus (types 1, 2, and 3) Ab titers ≥ 1:8" has been added in the SAP for Stage 2 infants / post-Dose 4 (it was not mentioned in the protocol).

6 References List

1 Rüggeberg JU, Gold MS, Bayas J-M, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84

2 Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-7