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.

Clinical Study Protocol, Amendment 4

Health Authority File Number(s):	BB-IND #: 018207
WHO Universal Trial Number (UTN):	U1111-1238-1638
Study 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
Manufacturer:	SK bioscience Co., Ltd 310, Pangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, Korea [13494]
Coordinating Investigator (Stage I)	[redacted]
Coordinating Investigator (Stage II)	

Sponsor's Responsible Medical Officer:	[redacted]
Global Clinical Development Strategy Expert:	
Global Safety Officer:	
Regional Trial Manager:	

Version and Date of the Protocol: Version 6.0 dated 04 April 2022

History of Protocol Versions

Version*	Date	Comments
1.0	09 January 2020	Version submitted to the IEC/IRB. Updated in response to comments provided by the Health Authorities (CBER) prior to study initiation.
2.0	15 April 2020	Version submitted to the IEC/IRB First version used in the study at the time of FVFS
3.0	30 November 2020	Version submitted to the IEC/IRB Amendment 1
4.0	21 April 2021	Version submitted to the IEC/IRB Amendment 2
5.0	25 June 2021	Version submitted to the IEC/IRB Amendment 3

*Versions in bold font have been approved by IEC/IRB and used in the study

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Synopsis

Company:	Sanofi Pasteur
Investigational Product:	SP0202 - 21–valent pneumococcal conjugate vaccine
Active Substances:	*Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F

Title of the Study:	Safety and Immunogenicity of a Pneumococcal Conjugate Vaccine (PCV) when Administered Concomitantly with Routine Pediatric Vaccines in Healthy Toddlers and Infants
Development Phase:	Phase II
Coordinating Investigator (Stage I):	[redacted]
Coordinating Investigator (Stage II):	
Study Sites:	This will be a multi-center study conducted at approximately 42 sites in the United States (US), 8 sites in Canada and 2 sites in Honduras Investigators and sites will be listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Quarter 2 of 2020 (first visit of the first subject) to Quarter 2 of 2023 (last contact of the last subject)
Study Design, Schedule of Study Procedures, and Methodology:	This will be a Phase II, randomized, active-controlled, observer-blind (double-blind across investigational vaccine formulations), age de-escalating, multi-centered study to assess the safety and the immunogenicity of 3 different formulations of an investigational pneumococcal conjugate vaccine (PCV) in approximately 140 healthy toddlers (12–15 months of age [MoA]), and 700 healthy infants (aged 42 to 89 days). The vaccine is referred to as SP0202 in what follows. The study will involve 2 stages: • 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 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 1): • Pentacel (DTaP-IPV/Hib) at 2, 4, 6 months of age* • 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
	* Dose 4 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.

Note 1: In addition to routine vaccines 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.

Note 2: Other pediatric vaccines (eg, hepatitis A, meningitis C) should be administered after the completion of the last study visit. They will be considered as out of the scope of the study and will not be provided by the Sponsor but procured by the sites as per standard practices.

Table 1: 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.

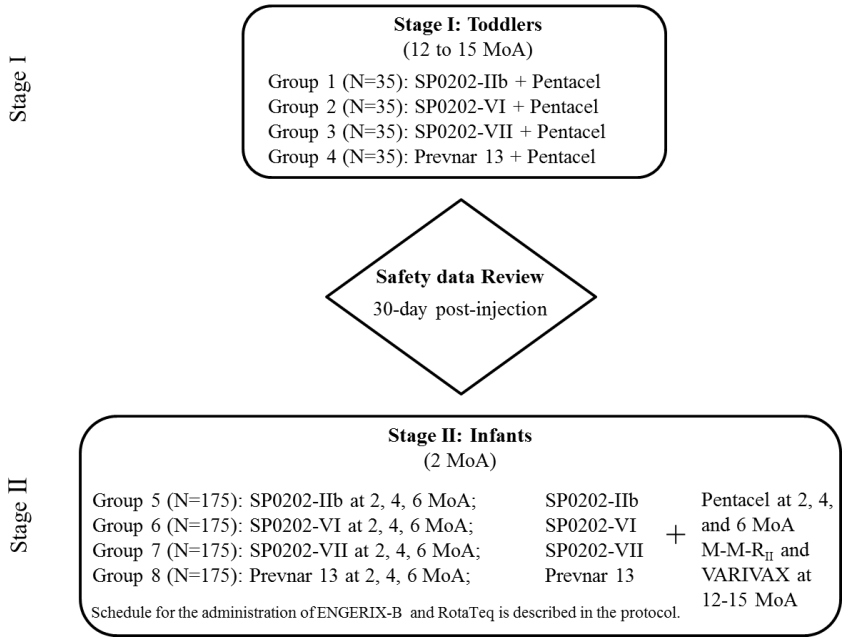
‡ ENGERIX-B (Purified Recombinant Hepatitis B Surface Antigen; GlaxoSmithKline Inc.). Hepatitis B vaccination can be administered concomitantly with Pentacel and PCV doses at V01, V02, and V03.

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

A total of 140 subjects (35 subjects 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 subjects (175 subjects 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), as shown in Figure 1.

Figure 1: Overview of the step-down enrollment



Randomization:

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

Visits and Phone Contacts:

During Stage I there will be 2 planned visits for toddlers (Groups 1-4). During Stage II there will be 6 planned visits for infants (Groups 5-8).

Subjects' parents / guardians will be contacted by phone 8 days [+2 days] after each vaccine injection, and 6 months [+14 days] after the last vaccine injection.

Injection:

Toddlers will receive 1 dose of either one SP0202 formulation or Prevnar 13 and 1 dose of Pentacel concomitantly at 12-15 MoA.

Infants will receive 1 dose of either one SP0202 formulation or Prevnar 13 at 2, 4, 6, and 12-15 MoA. Pentacel, RotaTeq, M-M-RII, and VARIVAX doses will be administered concomitantly with the PCV doses. ENGERIX-B can be administered concomitantly with Pentacel and PCV doses at V01, V02, and V03.

Blood sampling:

During Stage I, all toddlers will provide 2 blood samples (BLs; 6 mL each) for the assessment of SP0202 and DTaP-IPV/Hib antigens (Pentacel) immunogenicity: a first sample before injection (BL0001) and a second sample (BL0002) at D30 [+14 days] post-injection.

During Stage II, all infants will provide 3 or 4 blood samples for the assessment of study and pediatric vaccines' immunogenicity: a sample before injection (BL0001; 3 mL) at D0*, a sample 1 month after PCV Dose 3 (BL0002; 6 mL) at D150 [±14 days] (Visit 4 [V04]), a sample before PCV Dose 4 (BL0003; 6 mL) at D300 [±14 days] (V05), and a sample 1 month after PCV Dose 4 (BL0004; 6 mL) at D330 [+14 days].

* Not applicable from protocol Version 5.0

	Immunogenicity Immunogenicity of SP0202 formulations and Prevnar 13 will be assessed through the measurement of serotype specific type G immunoglobulin (IgG) and opsonophagocytic activity (OPA) of pneumococcal serotypes. IgG concentrations for all pneumococcal serotypes included in each of the SP0202 formulations and Prevnar 13 will be measured in all subjects. OPA will be measured in all toddlers enrolled in Stage I and in a random subset of 125 infants per group (depending on the available serum volume) enrolled in Stage II in samples collected 1 month after Dose 3, and pre- and post-dose (PD) 4. For toddlers, the immunogenicity of Pentacel will be assessed 1 month after injection. For infants, the immunogenicity of concomitant vaccines will be assessed 1 month after the last injection in the study, ie, 1-month PD3 for Pentacel, ENGERIX-B*, and RotaTeq; 1-month PD4 for M-M-R_{II} and VARIVAX. * Immunogenicity to ENGERIX-B will be presented according to the number of doses received ***Safety*** Reactogenicity data will be collected in all subjects after each injection. Injection site reactions will be collected for both study and concomitant pediatric vaccines. All subjects will be observed for 30 minutes after vaccination, and clinical site personnel will record any unsolicited systemic adverse events (AEs) occurring during that time as immediate unsolicited systemic AEs in the case report book (CRB). Subjects' parents / guardians will record in the diary card (DC) / electronic 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. Serious adverse events (SAEs) and adverse events of special interest (AESIs) will be collected throughout the study (from D0 until the 6-month follow-up safety phone contact). At Visit 2 (V02) for toddlers and Visit 5 (V05) for infants, all parents / guardians will be given a memory aid (MA) in which to record safety information. At approximately 6 months after injection, the clinical site personnel will contact each subject's parents / guardians by phone to obtain information about SAEs and AESIs. **Note:** For both toddlers and infants, anaphylaxis/hypersensitivity, convulsions (including febrile convulsions), hypotonic-hyporesponsive episode, and apnea will be considered as AESIs
Early Safety Data Review:	The safety of investigational products will be continuously monitored by the Sponsor. An ESDR will be performed, the goal of which is to allow for a cautious, stepwise approach to vaccine administration. [redacted] The safety data collected will be entered into the CRB and summarized by the Sponsor. A blinded review will be performed by the Sponsor during the Safety Management Team (SMT) meetings. An unblinded review by the independent DMC will also be conducted. It is understood that this review is based on

	preliminary data that have not been subject to validation and database lock. The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined early interim safety analysis will continue unchanged. The following safety parameters will be assessed as part of the ESDR: • Immediate unsolicited systemic AEs • Solicited injection site and systemic reactions • Unsolicited AEs reported as related by the Investigator • SAEs • AESIs Enrollment of infants will not begin until the end of the review. In addition, the data will be examined for the following: • Any deaths, regardless of causality • Any vaccine-related SAEs • Any AESIs • Any signs of injection site necrosis or exfoliative dermatitis • Grade 3 fever reported in more than 10% of subjects; presence of concurrent infectious disease will be documented If any of the above criteria are met, a decision based on the SMT and DMC recommendations will be made as to whether enrollment of infants will be allowed to begin or whether any adjustments ought to be done. The DMC will review the unblinded data by group to be able to identify any trend for differences between each SP0202 formulation and Prevnar 13 for each safety criterion and overall safety profile. The DMC may recommend removing 1 or more SP0202 formulation from Stage II. Further details will be provided in the DMC Charter (before the start of trial). Moreover, the option of partial or full unblinding can be available to the Sponsor through an independent statistician, if required, for a further in-depth review of the data. The Sponsor's SMT is empowered to recommend a pause in recruitment while it investigates any potential signal or concern. The clinical team and SMT will review the data being generated from the study at regular intervals for any new safety signals or safety concerns.
Interruption of the Study	The study may be discontinued as per ESDR decision or if new data about the investigational product resulting from this study or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, Independent Ethics Committees / Institutional Review Boards (IECs/IRBs), or the governing regulatory authorities in the United States, Canada, and Honduras. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the study subjects' parents / guardians and should assure appropriate subject therapy and/or follow-up.
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 1-4) • 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 5-8) • 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 5-8)
Primary Endpoints:	***Safety:*** The following endpoints will be used for all subjects for the evaluation of the Safety Objectives: • 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 subject'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. Other endpoints will be recorded or derived as described in the statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activity [MedDRA] preferred term), time of onset, duration, number of days of occurrence, Grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome. ***Immunogenicity:*** **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 subjects 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
Secondary Objectives	***Immunogenicity of SP0202 or Prevnar 13:*** • To assess the immune response (serotype specific OPA titer) of the SP0202 formulations and Prevnar 13 1 month after the administration of one dose in toddlers (Groups 1-4) • 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 5-8) • 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 5-8) ***Immunogenicity of concomitant licensed vaccines when co-administered with SP0202 or Prevnar13:*** **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 PD3 for ENGERIX-B†, RotaTeq, and Pentacel; at PD4 for M-M-R_{II} and VARIVAX]) * Not applicable from protocol Version 5.0 † Immunogenicity to ENGERIX-B will be presented according to the number of doses received
Secondary Endpoints:	***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 activity (MOPA), at baseline and 30 days post-injection • Percentage of subjects 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 subjects 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 ***Immunogenicity of concomitant licensed vaccines when co-administered with SP0202 or Prevnar13:*** **Toddlers** Before vaccination (D0) in all subjects: • Anti-pertussis (PT [pertussis toxoid / toxin], 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 subjects: • 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 subjects (D0)*: • Anti-rotavirus serum immunoglobulin (Ig) A Ab concentrations • Anti-pertussis (PT, FHA, PRN, and FIM) Ab concentrations • Anti- diphtheria toxoid Ab concentrations • Anti- tetanus toxoid Ab concentrations * Not applicable from protocol Version 5.0

<table>
<tr><td></td><td>
<u>One month after 6 MoA vaccination (D150) in all subjects:</u>
• 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
* Not applicable from protocol Version 5.0

<u>One month after 12-15 MoA vaccination (D330-D420) in all subjects:</u>
• Anti-measles Ab concentrations
• 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
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<tr><td>Planned Sample Size:</td><td>
A total of 840 subjects are planned to be enrolled, 140 toddlers and 700 infants.
Stage I – Toddlers
<table>
<tr><th>Groups</th><th>Number of subjects</th><th>Vaccine formulation / treatment</th></tr>
<tr><td>Group 1</td><td>35</td><td>SP0202-IIb</td></tr>
<tr><td>Group 2</td><td>35</td><td>SP0202-VI</td></tr>
<tr><td>Group 3</td><td>35</td><td>SP0202-VII</td></tr>
<tr><td>Group 4</td><td>35</td><td>Prevnar 13</td></tr>
</table>
Stage II – Infants
<table>
<tr><th>Groups</th><th>Number of subjects</th><th>Vaccine formulation /treatment</th></tr>
<tr><td>Group 5</td><td>175</td><td>SP0202-IIb</td></tr>
<tr><td>Group 6</td><td>175</td><td>SP0202-VI</td></tr>
<tr><td>Group 7</td><td>175</td><td>SP0202-VII</td></tr>
<tr><td>Group 8</td><td>175</td><td>Prevnar 13</td></tr>
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Duration of Participation in the Trial:	**Toddlers** The duration of each subject's participation in the study will be approximately 6 months for subjects enrolled in Groups 1, 2, 3, and 4. **Infants** The duration of each subject's participation in the study will be approximately 16 to 19 months for subjects enrolled in Groups 5, 6, 7, and 8.
Investigational Products:	
Investigational Product 1:	SP0202-IIb – PCV; SK bioscience Co., Ltd.
Form:	Liquid, suspension
Composition:	Each 0.5 mL dose of vaccine will contain: Active ingredients: [redacted]
Route:	Intramuscular (IM)
Batch Number:	TBD
Investigational Product 2:	SP0202-VI – PCV; SK bioscience Co., Ltd.
Form:	Liquid, suspension
Composition:	Each 0.5 mL dose of vaccine will contain: Active ingredients: [redacted]

	[redacted]
Route:	IM
Batch Number:	TBD
Investigational Product 3:	SP0202-VII – PCV; SK bioscience Co., Ltd.
Form:	Liquid, suspension
Composition:	Each 0.5 mL dose of vaccine will contain: Active ingredients:
	[redacted]
Route:	IM
Batch Number:	TBD
Control Product:	Prevnar 13®, (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]); Pfizer Inc.
Form:	Liquid
Composition:	Each 0.5 mL dose of vaccine contains: Active ingredients: 2.2 µg of polysaccharide from *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F, and 4.4 µg of polysaccharide for serotype 6B, individually conjugated to cross-reacting material 197 (CRM_{197}) approximately 34 µg of CRM_{197} Other ingredients: NaCl, succinic acid, polysorbate 80, water-for-injection Adjuvant: 0.125 mg of aluminum
Route:	IM
Batch Number:	Commercial Lot
Other Product 1:	Pentacel® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate [Tetanus Toxoid Conjugate] vaccine); Sanofi Pasteur Ltd.
Form:	DTaP-IPV Liquid used to reconstitute lyophilized PRP-T

Composition:	Each 0.5 mL dose contains: Each 0.5 mL dose contains: Diphtheria toxoid ..... 15 Limit of Flocculation (Lf) Tetanus toxoid ..... 5 Lf Acellular pertussis antigens: Pertussis toxin (PT) .....20 µg Filamentous hemagglutinin (FHA).....20 µg Pertactin (PRN).....3 µg Fimbriae Types 2 and 3 (FIM).....5 µg Inactivated polioviruses: Type 1 (Mahoney) .....40 D-antigen units (DU) Type 2 (MEF-1).....8 DU Type 3 (Saukett) .....32 DU *H. influenzae* type b (PRP) .....10 µg Tetanus toxoid (PRP-T).....24 µg Adjuvant: 0.33 mg of aluminum
Route:	IM
Batch Number:	Commercial Lot
Other Product 2:	ENGERIX-B® (Hepatitis B Vaccine [Recombinant]); GlaxoSmithKline.
Form:	Liquid
Composition:	Each 0.5 mL dose contains 10 µg of hepatitis surface antigen
Route:	IM
Batch Number:	Commercial lot
Other Product 3:	RotaTeq® (Rotavirus Vaccine, Live, Oral, Pentavalent); Merck & Co, Inc.
Form:	Liquid
Composition:	Each 2 mL dose contains: G1 serotype.....2.2 x 10^6 infectious units G2 serotype.....2.8 x 10^6 infectious units G3 serotype.....2.2 x 10^6 infectious units G4 serotype.....2.0 x 10^6 infectious units P1A(8).....2.3 x 10^6 infectious units The reassortants are suspended in a buffered stabilizer solution.
Route:	Oral
Batch Number:	Commercial Lot
Other Product 4:	M-M-R®$_{II}$ vaccine (Measles, Mumps, and Rubella Virus Vaccine Live); Merck & Co, Inc.
Form:	Liquid
Composition:	Each 0.5 mL dose contains: Measles virus (derived from Ender's Edmonston strain) propagated in chick embryo cell culture — not less than 1000 $TCID_{50}$* Mumps virus (Jeryl Lynn™ [B level] strain) propagated in chick embryo cell culture — not less than 12 500 $TCID_{50}$* Rubella virus (Wistar RA 27/3 strain) propagated in WI-38 human diploid lung fibroblasts — not less than 1000 $TCID_{50}$* *$TCID_{50}$ = tissue culture infectious doses 50%

Route: *Batch Number:*	Subcutaneous Commercial Lot
Other Product 5: *Form:* *Composition:* *Route:* *Batch Number:*	VARIVAX® (Varicella Virus Vaccine Live); Merck & Co, Inc. Liquid Each 0.5 mL dose contains not less than 1350 plaque-forming units (PFU) of Oka/Merck varicella virus Subcutaneous Commercial Lot
Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: **Toddlers and infants** 1) Informed consent form has been signed and dated by the parent(s) or other guardian, and by an independent witness, if required by local regulations 2) Subject and parent/guardian are able to attend all scheduled visits and to comply with all study procedures 3) Born at full term of pregnancy (≥ 37 weeks) and/or with a birth weight ≥ 5.5 lbs or 2.5 kg 4) Healthy toddlers / infants as determined by medical history, physical examination, and judgment of the Investigator **Specifically for toddlers** 5) Aged 12 to 15 months on the day of the first study visit[a] 6) Subject has received 3 doses of Prevnar 13 and 3 doses of diphteria, tetanus, acellular pertussis, poliovirus, and *Haemophilus influenzae* type b antigens in infancy **Specifically for infants** 7) Aged 42 to 89 days on the day of the first study visit[b] [a] "12 to 15 months" means from the 12th month after birth to the day before the 16th after birth b "42 to 89 days" means the 42th day after birth to the day before the 90th day after birth
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: **Toddlers and infants:** 1) Participation at the time of study enrollment (or in the 4 weeks preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure 2) Family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated 3) Blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems 4) Active tuberculosis 5) History of *S. pneumoniae* infection or disease, confirmed either serologically or microbiologically 6) History of any neurologic disorder, including any seizures and progressive neurologic disorders 7) History of Guillain-Barré syndrome

	8) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances 9) Verbal report of thrombocytopenia contraindicating intramuscular vaccination in the Investigator's opinion 10) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination in the Investigator's opinion. 11) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw 12) Chronic illness (including, but not limited to, cardiac disorders, congenital heart disease, chronic lung disease, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and know congenital or genetic diseases) that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion 13) Any condition which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives 14) In an emergency setting, or hospitalized involuntarily 15) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C / ≥ 100.4°F). A prospective subject should not be included in the study until the condition has resolved or until 3 days after the febrile event has resolved 16) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study **Specifically for toddlers:** 17) Receipt of any vaccine in the 4 weeks preceding the study vaccination or planned receipt of any vaccine from enrollment through the last blood sampling Visit (Visit 2), except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines 18) Receipt of immune globulins, blood or blood-derived products in the past 3 months 19) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months) 20) History of diphtheria, tetanus, pertussis, poliomyelitis, and/or *H. influenzae* type b infection or disease **Specifically for infants:** 21) Receipt of any vaccine in the 4 weeks preceding the study vaccination or planned receipt of any vaccine from enrollment through the last blood sampling Visit (Visit 6), except for influenza vaccination or COVID-19 vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines, and COVID-19 vaccines, as applicable per local recommendations 22) Receipt of immune globulins, blood or blood-derived products since birth

	23) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth 24) Previous vaccination against *S. pneumoniae* 25) Previous vaccination against the following antigens: diphteria, tetanus, pertussis, *H. influenzae* type b, poliovirus, rotavirus, measles, mumps, rubella, and varicella 26) Receipt of more than 1 previous dose of hepatitis B vaccine 27) History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, measles, mumps, rubella, varicella, *H. influenzae* type b, and/or rotavirus infection or disease 28) History of intussusception
Statistical Methods:	Statistical analyses will be performed on safety and immunogenicity data collected for each stage as follows: • 1 unblinded analysis on immunogenicity and safety data collected in toddlers (Stage I) up to V02 and including 6-month follow-up data if available at the time of V01-V02 immunogenicity data release • 1 unblinded analysis on immunogenicity data (serotype specific IgG concentration) collected on the first 350 randomized infants (Stage II) up to 1 month after the third dose of PCV • 1 unblinded analysis on data collected in infants (Stage II) up to 1 month after the third dose of PCV and including Stage I data of the 6-month follow-up (if not done as part of first analysis). The analysis may be conducted in two steps depending on the duration of immunogenicity testing: 1 – an early analysis on safety and serotype specific IgG results (primary endpoints) of all subjects up to 1 month after the third dose; 2 – an analysis on all results (primary and secondary endpoints) up to 1 month after the third dose • 1 unblinded analysis on immunogenicity and safety collected in infants (Stage II) up to 1 month after the fourth dose of PCV. The 6-month safety follow-up data will be included, depending on the timing of this analysis. • 1 final analysis on complete Stage II data including the 6-month follow-up, if needed. ***Analyses*** All analyses will be descriptive; no hypotheses will be tested. The per-protocol population and the Full Analysis Set will be used for the immunogenicity analyses and the safety population will be used for the safety analyses. For the main parameters, 95% confidence intervals (CIs) of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions. CIs of the difference of proportions between 2 groups will be computed using the Wilson Score method without continuity correction. CIs of ratio of geometric mean titers (GMTs) / GMCs between 2 groups will be computed from the difference in means of log10 transformed titers/concentrations between 2 groups with normal approximation.

Primary Objectives

Safety

Safety profile of each group will be described after each and any vaccination using counts and percentages. The 95% CIs may also be displayed.

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 concentrations, GM of concentrations ratio (post- / pre-vaccination)

Immunogenicity – Stage II (infants)

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

- Percentage of subjects with a PD3 and PD4 serotype specific concentration ≥ 0.35 µg/mL
- GM of serotype specific concentrations (pre-dose 1*, PD3, pre-dose 4, PD4)
- GM of serotype specific concentrations ratio (PD3/pre-dose 1* and PD4/pre-dose 4)

* Not applicable from protocol Version 5.0

[redacted]

Further analyses may be described in the Statistical Analysis Plan (SAP).

Secondary Objectives

Immunogenicity – 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 subjects with a post-vaccination serotype specific titers above or equal to LLOQ

Immunogenicity of concomitant vaccines:

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 subjects with concentration / titer above predefined threshold, including those defining seroprotection
- Vaccine response for pertussis (PT, FHA, PRN, and FIM) antigens

Immunogenicity – 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 random OPA subset for each pneumococcal serotype specific OPA titers:

- Percentage of subjects with a PD3 and PD4 serotype specific titers 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)

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-R_{II}, and VARIVAX) antigens:

- GM of concentrations / titers for all antigens (at pre-Dose 1* for RotaTeq, and diphtheria, tetanus, and Pertussis antigens; at PD3 for ENGERIX-B†, RotaTeq, and Pentacel; at PD4 for M-M-R_{II} and VARIVAX)
- Percentage of subjects with concentrations / titers above predefined thresholds, including those defining seroprotection (at PD3 and PD4 as applicable)

* Not applicable from protocol Version 5.0

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

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

Sample size:

The number of subjects 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 subjects per group (140 toddlers) in Stage I and 175 subjects 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 subjects per group is anticipated for toddlers, infants at PD3, and infants at PD4, respectively.

[redacted]

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 subject

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 subject 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 subject.

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

‡ During this call the staff will determine whether the subject experienced any SAE and AESI not yet reported. The site staff will remind subject'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 subject's parent / guardian and determine whether the subject experienced any SAE or AESI not yet reported.

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-R$_{II}$, and VARIVAX [as per pediatric schedule]), 4 blood samples, approximately 16 to 19 Months Duration per Subject

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 subjects (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 subject 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	X		X		X			-			
ENGERIX-B§	X		X		X			-			
RotaTeq	X		X		X			-			
M-M-R$_{II}$ and Varivax	-		-		-			X			

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 subjects (months)	2		4		6		7	12-15		13-16	18 - 21
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 subject 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 subject.

‡ 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 subject experienced any SAE or AESI not yet reported. The site staff will remind subject's parent / guardian to continue using the DC.

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

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-R$_{II}$, and VARIVAX [as per pediatric schedule]), 3 blood samples, approximately 16 to 19 Months Duration per Subject

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 subjects (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 subject 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	X		X		X			-			
RotaTeq	X		X		X			-			
M-M-R$_{II}$ and Varivax	-		-		-			X			

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 subjects (months)	2		4		6		7	12-15		13-16	18 - 21
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 subject 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 subject.
‡ 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 subject experienced any SAE or AESI not yet reported. The site staff will remind subject's parent / guardian to continue using the DC.
†† During this call the staff will review the MA with the subject's parent / guardian and determine whether the subject experienced any SAE and AESI not yet reported.

List of Abbreviations

AAP	American Academy of Pediatrics
Ab	antibody
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
Ag	antigen
AR	adverse reaction
BL	blood sample
CBER	Center for Biologics Evaluation and Research
CDM	Clinical Data Management
CFL	Clinical Franchise Leader
CI	confidence interval
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CRB	(electronic) case report book [all the case report forms for a subject]
CRF	(electronic) case report form
CRM_{197}	cross-reacting material 197, a non-toxic mutant of diphtheria toxin
CTA	clinical trial agreement
CTL	Clinical Team Leader
D	day
DC / eDC	diary card / electronic diary card
dil	dilution
DMC	data monitoring committee
DMF	N, N-dimethylformamide
DOD	delta optical density
DTaP	diphtheria, tetanus, and acellular pertussis
DTP	diphtheria, tetanus, and pertussis
ECL	electro-chemiluminescence assay
ELISA	enzyme-linked immunosorbent assay
ESDR	early safety review
EDC	electronic data capture
EIA	enzyme immunoassay
EU	endotoxin units
FAS	full analysis set
FDA	Food and Drug Administration

FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GM	geometric mean
GMC	geometric mean concentration
GMCR	geometric mean concentration ratio
GMT	geometric mean titer
gp	glycoprotein
GPV	Global Pharmacovigilance
HB	hepatitis B
HBs	hepatitis B surface
Hib	*Haemophilus influenza b*
HIV	human immunodeficiency virus
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	immunoglobulin type A
IgG	immunoglobulin type G
IM	intramuscular
IME	important medical event
IND	investigational new drug (application)
IPD	invasive pneumococcal disease
IRB	Institutional Review Board
IRT	interactive response technology
IU	international units
JL135	Jeryl Lynn 135
LCLS	last contact, last subject
LLOQ	lower limit of quantification
LLT	lowest level term
MA	memory aid
MedDRA	Medical Dictionary for Regulatory Activities
mIU	mili-international units
mL	milliliter

M-M-R	measles, mumps, rubella
MMRV	measles, mumps, rubella & varicella
MoA	months of age
MOPA	multiplex opsonophagocytic activity
MTL	Medical Team Leader
NSAID	non-steroidal anti-inflammatory drug
OD	optical density
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
PD	post-dose
PFU	plaque-forming unit
PnPS	pneumococcal capsular polysaccharide
PPAS	per-protocol analysis set
PRN	pertactin
PRP	polyribosyl-ribitol phosphate
PT	pertussis toxoid / toxin
RCDC	reverse cumulative distribution curves
RIA	radioimmunoassay
RLU	relative light units
RMO	Responsible Medical Officer
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous
SCID	Severe Combined Immunodeficiency Disease
SK	SK bioscience Co., Ltd.
SMT	Safety Management Team
TCC	tissue culture control
$TCID_{50}$	tissue culture infectious doses 50%
TMF	trial master file
TTxd	tetanus toxoid
ULOQ	upper limit of quantification
U	units
V	visit
VZv	varicella-zoster virus
WHO	World Health Organization
WT	wild type

1 Introduction

1.1 Background

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.

S. pneumoniae (or pneumococcus) is a Gram-positive diplococcus, encapsulated with a diverse range of polysaccharides. Based on the differences in the polysaccharide capsule, 98 different serotypes of *S. pneumoniae* have been described (1) (2) (3). The most common disease-causing serotypes observed in different countries and / or geographic regions are generally similar; however, there may be large variations in relative serotype prevalence in these areas, particularly between developed and developing countries.

The microorganism, through the asymptomatic colonization of the nasopharynx, is a major cause of a number of infections, including pneumonia, meningitis, bacteremia, sinusitis, and otitis media (3). Infections characterized by the isolation of *S. pneumoniae* from a normally sterile site, such as blood, cerebrospinal fluid, pleural fluid, or synovial fluid, are identified as occurrences of invasive pneumococcal disease (IPD).

Pneumococcal conjugate vaccines (PCVs) have been shown to be effective in preventing pneumococcal pneumonia, IPD, and otitis media in children (4) (5) (6) (7) (8) (9). Ever since the introduction of a 7-valent PCV in 2000[a], the overall number of IPD cases, especially the number of cases due to serotypes covered by the vaccine, has been declining (10) (11). Strengthening this trend, the introduction of a 10-valent PCV (2009)[b] and a 13-valent PCV (2010)[c] has confirmed the indirect benefit generated by reduction both in carriage of vaccine serotypes (ie, herd immunity in unvaccinated population) and in antimicrobial resistance (11) (12) (13). PCVs have had an important impact on public health in developed countries, as well as worldwide, since global roll out (14).

However, it is now acknowledged that serotypes covered by marketed PCVs tend to be replaced as pathogens by other circulating serotypes (15) (16). Less fit or emergent serotypes simply take advantage of an ecological niche left vacant (17). One of the most notable examples is serotype 19A which emerged as a predominant serotype in several countries, in both children and adults, after the introduction of PCV7, as well as in other countries with no PCV7 vaccination programs (18).

Currently, few strategies aiming to mitigate this phenomenon of serotype replacement are being developed. One possible solution would be to design a vaccine that combines 2 classes of

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[a] Prevnar®. Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), Pfizer Inc.

[b] Synflorix™. Pneumococcal conjugate vaccine (Non-typeable Haemophilus influenzae [NTHi] protein D, diphtheria or tetanus toxoid conjugates) adsorbed; GlaxoSmithKline Biologicals S.A.

[c] Prevnar® 13. Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]), Pfizer Inc.

complementary antigens, one to prevent colonization (ie, pneumococcal polysaccharides) and another to limit virulence transition (ie, protein antigens that selectively target pneumococci virulence transition) (19). Another possible solution is to introduce a PCV that includes a higher number of serotypes to cover the emerging ones and hence to protect against a higher number of pneumococcal strains causing invasive disease.

Sanofi Pasteur has decided to move forward with the latter approach, a next generation PCV comprising 21 serotypes (PCV21). Such a vaccine candidate has the potential to address important medical and public health needs by providing broader coverage for the leading serotypes associated with pneumococcal diseases.

1.2 Background of the Investigational Product

Sanofi Pasteur is developing a PCV21 (internal vaccine name is SP0202) 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). [redacted]

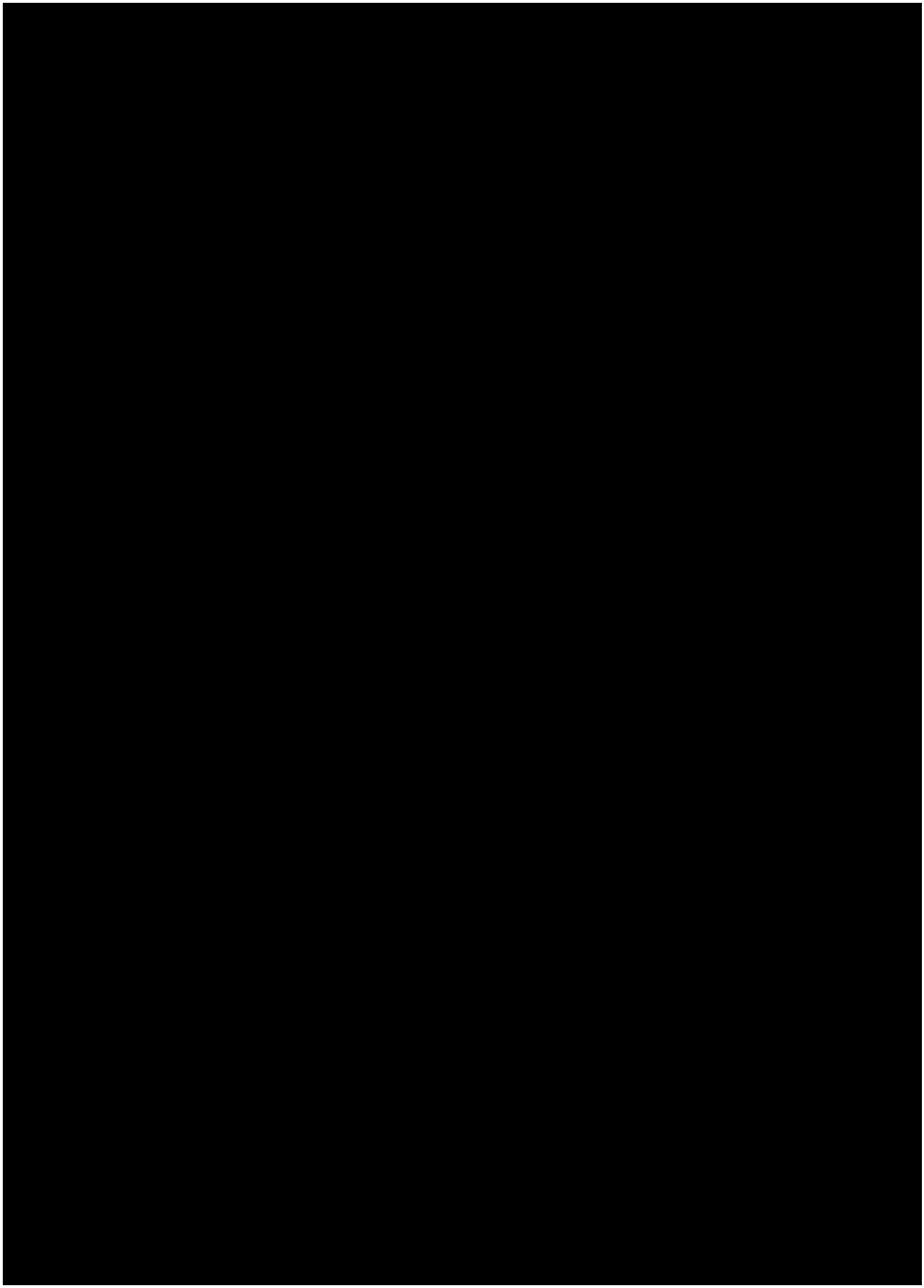
This vaccine is developed in partnership with SK bioscience Co., Ltd (South Korea) who has developed a 13-valent formulation comparable to Prevnar 13 vaccine in terms of serotypes composition and carrier protein (nontoxigenic variant of diphtheria toxin, referred to as CRM_{197}). [redacted]

[redacted]

Table 1.1: Specificities of the 4 formulations evaluated in Phase I study PSK00007

Formulation name	Formulation specificities
SP0202-I	[redacted]
SP0202-II	
SP0202-III	
SP0202-IV	

This study was carried out in healthy adults aged 19 to 49 years old in the US. No safety concerns were identified for any SP0202 formulations; the safety profile of the formulation SP0202-II containing 4 serotypes conjugated to tetanus toxoid was unremarkable compared to the 3 other SP0202 formulations. [redacted]



1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

As mentioned previously, 4 formulations of SP0202 investigational vaccine were evaluated in Phase I clinical study (PSK00007) that was carried out in healthy adults aged 19 to 49 years old in the US. [redacted] and the available data support the evaluation in the pediatric population. It is expected that the toddlers and infants who will be vaccinated with SP0202 will develop an immune response against the 21 serotypes (the 13 pneumococcal serotypes common with Prevnar 13 as well as the new 8 additional serotypes), although there is no guarantee.

Subjects who will receive Prevnar 13 will likely be protected against pneumococcal disease due to 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

Apart from protection against pneumococcal disease, infants will be vaccinated with routine licensed vaccines and will benefit from protection against different diseases: measles, mumps, rubella, varicella, rotavirus infection, hepatitis B, diphtheria, tetanus, pertussis, polio, and invasive disease caused by *Haemophilus influenzae* type b bacteria.

As with any vaccines, SP0202 formulations and Prevnar 13, as well as the concomitant routine vaccines administered during the study may not protect 100% of individuals against the disease they are designed to prevent.

1.3.2 Potential Risks to Subjects

Like other vaccines, SP0202, Prevnar 13, and other routine licensed vaccines included in this study may cause injection sites reactions such as pain, swelling, and erythema, or certain systemic events such as fever, irritability, drowsiness, loss of appetite, abnormal crying, decreased sleep, and vomiting when administered to infants/toddlers.

No safety concerns were identified for any SP0202 formulations evaluated in the Phase I study; [redacted]

There may be a rare possibility of an allergic reaction which could be severe. Prior to any vaccine injection, all known precautions should be taken to prevent hypersensitivity reactions. This includes a review of the subject's prior vaccination history with respect to possible hypersensitivity to the vaccine or similar vaccines. Epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be available to treat unexpected reactions (eg, anaphylaxis).

There may be other risks for SP0202 which are not yet known.

To this day, there is no adequate evidence to clearly demonstrate the causal relationship between TTxd-containing vaccines and Guillain-Barré syndrome (29). The Institute of Medicine found evidence in favor of a causal relation between TTxd-containing vaccines and brachial neuritis (30). Arthus reactions are rarely reported after vaccination and can occur after TTxd-containing vaccines (31).

The potential risks listed here are not exhaustive. Refer to the Investigator's Brochure of the investigational vaccine and to the package inserts of Prevnar 13 (32) and concomitant licensed vaccines (33) (34) (35) (36) (37) for additional information regarding potential risks.

1.4 Rationale for the Study

The purpose of SP0202 investigational vaccine is to provide a broad coverage against pneumococcal serotypes. Compared to the licensed vaccine Prevnar 13, SP0202 investigational vaccine contains 21 serotypes with different content (13 serotypes common to those of Prevnar 13 and 8 additional serotypes) that are conjugated to 2 different protein carriers, either TTxd or CRM_{197}. In general, unconjugated bacterial polysaccharides are T-cell independent immunogens. Children under 2 years of age cannot mount effective responses against T-cell independent antigens, thus, they respond poorly to pneumococcal polysaccharides vaccine which contains native pneumococcal polysaccharides only (38). Therefore, the conjugation technology using a carrier protein to polysaccharides has been used to increase immunogenicity in infants and toddlers. Protein carrier specific T-cells provide the signal needed for maturation of the B-cell response and generation of B-cell memory, and production of high-affinity antibodies. Two protein carriers are included in the PCV21 formulation, both with proven safety records.

Based on PSK00007 results, 3 formulations have been selected for further evaluation in the target populations and secure the identification of a lead formulation for Phase III studies. These 3 formulations will be evaluated in this Phase II study.

The SP0202 investigational vaccine is designed for the immunization of infants/toddlers and elderly against pneumococcal disease. Toddlers aged 12-15 months, followed by infants aged 42 to 89 days will be included in the current Phase II study (PSK00008). It is also planned to evaluate the same formulations in a Phase II study in adults aged 50 years and above (PSK00009).

2 Study 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)

The endpoints for the safety objective are presented in Section 9.1.1.2.

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)

The endpoints for the immunogenicity objectives are presented in Section 9.1.2.1.

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-RII®, and VARIVAX®) when administered concomitantly with either SP0202 or Prevnar 13 (at pre-Dose 1[a] for RotaTeq, Diphteria, Tetanus, and Pertussis antigens; at post-dose 3 [PD3] for ENGERIX-B[b], RotaTeq, and Pentacel; at post-dose 4 [PD4] for M-M-RII and VARIVAX])

The endpoints for the secondary objectives are presented in Section 9.2.2.1

[a] Not applicable from protocol Version 5.0

[b] Immunogenicity to ENGERIX-B will be presented according to the number of doses received

3 Investigators and Study Organization

This study will be conducted in approximately 42 centers in United States, 8 centers in Canada and 2 centers in Honduras. The Principal Investigators and any sub-investigators at the individual sites will be coordinated by 1 Coordinating Investigator. Details of the study centers, the Investigators at each center, and the Coordinating Investigators are provided in the "List of Investigators and Centers Involved in the Trial" document.

An internal Safety Management Team (SMT) and a Data Monitoring Committee (DMC) will be implemented for this study.

[redacted]

In parallel, the DMC will conduct a formal unblinded review of the safety and will endorse, or not, the recommendation from the SMT whether to continue, modify, or stop the study for Stage II. A DMC charter will be developed before study start. It is understood that this review will be based on preliminary data, ie, data that have not been subject to validation and database lock.

The SMT may also review the data being generated from the study at regular intervals for any new safety signals or safety concerns.

Biostatistics, data management, monitoring, and medical writing will be either subcontracted to a contract research organization (CRO) or performed in house by the Sponsor.

The laboratories involved in this study will be:

- Sanofi Pasteur Global Clinical Immunology (GCI), Swiftwater (PA), USA: serotype specific immunoglobulin type G (IgG) concentrations for all pneumococcal serotypes, and anti-diphtheria antitoxin and anti-tetanus antitoxin concentrations
- [redacted]: serotype specific opsonophagocytic activity assay (OPA) titers for all pneumococcal serotypes as well as and anti-measles antibodies, anti-mumps antibodies, anti-rubella antibodies, and anti-varicella antibodies.
- [redacted] USA: anti-rotavirus serum immunoglobulin type A (IgA) antibody (Ab) concentrations

The role of Responsible Medical Officer (RMO), ie, the person having the authority to sign this protocol and any amendments on behalf of the Sponsor, is held jointly by [redacted]

4 Independent Ethics Committee / Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent forms (ICFs), subject recruitment procedures, and any other written information to be provided to subjects must be approved by,

and / or receive favorable opinion from, the appropriate Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).

In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and / or the Sponsor are responsible for obtaining this approval and / or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Investigator to the Sponsor together with the composition of the IEC / IRB (the names and qualifications of the members attending and voting at the meetings).

The Investigator or the Sponsor will submit written summaries of the status of the study to the IEC / IRB annually, or more frequently if requested. All serious adverse events (SAEs) occurring during the study that are related to the product administered will be reported by the Investigator to the IEC / IRB, according to the IEC / IRB policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study 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 5.1):

- 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

A total of 140 toddlers (35 subjects 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 subjects 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 5.1).

Table 5.1: Study Design

Stage I	
Toddlers (aged 12 to 15 months)	
140 subjects who have received a 3-dose primary series of Prevnar 13 and DTaP-IPV + Hib vaccines in infancy	35 subjects will receive 1 dose of SP0202-IIb and 1 dose of Pentacel concomitantly (Group 1)
	35 subjects will receive 1 dose of SP0202-VI and 1 dose of Pentacel concomitantly (Group 2)
	35 subjects will receive 1 dose of SP0202-VII and 1 dose of Pentacel concomitantly (Group 3)
	35 subjects will receive 1 dose of Prevnar 13 and 1 dose of Pentacel concomitantly (Group 4)
Stage II	
Infants (aged 2 months)	
525 subjects 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 subjects will receive 4 doses of SP0202-IIb (Group 5)
	175 subjects will receive 4 doses of SP0202-VI (Group 6)
	175 subjects will receive 4 doses of SP0202-VII (Group 7)
175 subjects will receive 3 doses of Prevnar 13, along with routine pediatric vaccines, at 2, 4, 6, and 12-15 months of age	175 subjects 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. [redacted]. 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. SAEs and AESIs[a] information will be collected throughout the study from V01 until the end of the study, ie, 6 month 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.

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

An Interactive Response Technology (IRT) will be used to assign subject 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 at each visit: 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)[a], 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 subjects. 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 (39). OPA will be measured on a subset of subjects.

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

5.1.2 Justification of the Study Design

PSK00008 is a Phase II study that will evaluate the safety and immunogenicity of 3 SP0202 formulations administered concomitantly with routine pediatric vaccines in infants and toddlers. A fourth group will serve as control and receive a dose of Prevnar 13 administered concomitantly with routine pediatric vaccines.

In the US as well as in Honduras and most provinces of Canada, pneumococcal vaccination with PCV13 (Prevnar 13) is routinely recommended in infants as a series of 3 doses, one dose at each of the following ages: 2, 4, and 6 MoA. A fourth dose is then administered when infants become toddlers at 12 through 15 MoA. To reflect this vaccination schedule, either one of the 3 SP0202 formulations or Prevnar will be administered concomitantly with routine pediatric vaccines in infants and toddlers in this study. Prevnar 13 has been selected as a comparator since this is the only marketed vaccine with 13 common serotypes with SP0202 investigational vaccine.

Routine vaccines schedules differ between the US, Honduras and Canada. Hep B vaccine is usually administered at birth, 2 and 6 MoA in the US, at 2, 4, and 6 MoA in some provinces of Canada and from Grade 6 or 7 in others, and at birth, 2, 4 and 6 MoA in Honduras. In this study, infants may receive the Hep B vaccine concomitantly with study vaccines at V01, V02, and V03 (a first dose of Hep B vaccine can be given at least 28 days prior to study enrollment). Administration of ENGERIX-B during the study visits will be documented in the eCRF.

[a] Not applicable from protocol Version 5.0

Additionally, routine vaccines schedule differs between Canadian territories. Meningococcal C vaccine is recommended at 12 MoA in Canada except in 3 Canadian territories (North West, British, and Yukon territories) where the vaccine should be administered at 2 MoA. To limit any bias from different vaccine co-administration schedule on safety and immunogenicity assessment, meningococcal C vaccine recommended at 12 MoA will be administered outside the study, after the completion of the last study visit or at least 4 weeks before the Dose 4 of study vaccines.

In line with the ACIP recommendation the measles, mumps, rubella & varicella (MMRV) vaccine is proposed as 2 separate vaccines since the risk of seizures is higher after MMRV injection than after separate M-M-R and varicella vaccines when given as the first dose of the series in younger children.

Given that this is a Phase II study aiming to document the safety and immunogenicity in pediatric population for the first time, PSK00008 study will involve 2 stages: a stage I in toddlers and after a review of the safety data of this stage, the stage II in infants will start.

Due to differences in the appearance of SP0202 and Prevnar13 products, the study will have an observer-blinded design (double-blind across SP0202 formulations) to limit any bias in the assessment of safety.

5.1.3 Study Plan

Enrollment

A total of approximately 140 subjects in Stage I and 700 subjects in Stage II will be enrolled. Eligible subjects will be identified and recruited, in accordance with inclusion / exclusion criteria. Each subject'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 [redacted] 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 the Stage I data review, the DMC may recommend dropping one or more SP0202 formulations before 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 5.2):

- 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. Dose 4 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 5.2: 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.

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], 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 (See Section 9.2.2.2)

Details about study visits are provided in Section 5.1.4 and the 2 tables of study procedures.

Safety

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

All subjects will be observed for 30 minutes after vaccination, and clinical site personnel will record any unsolicited systemic adverse events (AEs) occurring during that time as immediate unsolicited systemic AEs in the CRB.

Subjects' 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).

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

5.1.4 Visit Procedures

Toddlers

Visit 1 (Day 0): Inclusion, Randomization, Blood Sample, and Vaccination

1) Give the subject's parent / guardian information about the study, answer any of her / his questions, obtain written informed consent, and give her / him a signed copy.

2) Obtain significant medical history about the subject.

3) Check vaccination history.

[a] Not applicable from protocol Version 5.0

4) Obtain demographic data.

5) Check medications and record reportable medication ongoing at the time of inclusion.

6) Check inclusion and exclusion criteria for eligibility.

7) Conduct a physical examination, including, but not limited to, examination of the head (ear, nose, and throat), neck, heart, lungs, abdomen, and extremities. If a routine examination had been performed within the past week by a qualified health care provider, it does not need to be repeated unless there were changes in health status, in which case it may be limited to the affected area.

8) Take the subject's temperature. If the temperature is ≥ 38.0°C / ≥ 100.4°F, postpone vaccination until the condition is resolved.

9) If the subject is eligible, contact the IRT for randomization, to obtain a subject number, and vaccine allocation.

10) Obtain the first blood sample (BL0001 – 6 mL) for immunogenicity (see Section 7.1 for detailed instructions regarding the handling of blood samples).

    If the blood sample cannot be obtained, the parent/guardian should be given the opportunity to bring the subject back to the study site for another attempt, as long as the subject continues to remain eligible for the study. All attempts should be made to obtain a blood sample; however, if the attempts are unsuccessful, the subject could continue in the study.

11) Inject the following study vaccines. Each vaccine should be administered in an assigned location (see Operating Guidelines) and documented appropriately:

    - SP0202 or Prevnar 13: inject IM into the anterolateral area of the thigh, preferably the right thigh.
    - Pentacel: inject IM into the anterolateral area of the thigh, preferably the left thigh (ie, the opposite leg from that used for SP0202 or Prevnar).

12) Keep the subject under observation for 30 minutes, and report any reaction / event in the source document.

13) Record the date of injection, site, and side of injection, route of administration, as well as the dose number of the vaccine.

14) Give the parent / guardian a DC / eDC to record any injection site and systemic AEs, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of AEs. Remind parents to carefully report any clinical signs / diagnosis experienced at the same time as the fever episode > 39.5°C / 103.1°F.

15) Give the parent / guardian a thermometer for rectal temperature measurements, and a ruler to measure the size of any injection site reactions, and go over the instructions for their use.

16) Arrange an appointment for V02 (D30 + 14 days). Remind the parent / guardian to expect a telephone call 8 days after V01 and to bring back the DC / eDC when they return for V02 at a specified date and time.

17) Remind the parent / guardian to notify the site in case of serious medical event occurs.

18) Complete the source documents and relevant case report forms (CRFs) for this visit.

Telephone Call 1 (8 [+2] days after Visit 1)

Note: If D8 falls on a weekend or a holiday, the telephone call may be made on the following business day.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.

2) Remind the parent / guardian to do the following:
   - Complete the Day 0–7 pages of the DC / eDC
   - Complete the remaining pages of the diary card, and bring them to V02
   - Notify the site in case of an SAE

Visit 2 (30 [+14] days after Visit 1): Collection of Safety Information and Blood Sample

1) If the DC information from Day 0–7 has not yet been obtained / information from D0 – D7 not entered in eDC, obtain it at this time by interviewing the parents. Review the pages of the DC / eDC with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination.

2) Check medications and record reportable ongoing medications. Review temporary contraindications for blood sampling. Ensure the subject has not had any antibiotics within the previous 72 hours (3 days).

3) Conduct a physical examination and take the subject's temperature if necessary, based on the health status of the subject.

4) Obtain the second blood sample (BL0002 – 6 mL) (see Section 7.1 for detailed instructions regarding the handling of blood samples).

5) Complete the source document and the relevant CRFs for this visit.

6) Complete the end of study CRF of the CRB.

7) Provide the memory aid to the subject's parent / guardian.

Safety Follow-up Telephone Call (D180 + 14 days)

The investigator or authorized designee will:

1) Ask to the parent / guardian if the subject has experienced any SAE or AESI in the time since vaccination.
2) Complete the relevant CRF for this phone contact.

A follow-up visit can be arranged depending on the information recorded during the phone call.

Infants

Visit 1 (Day 0): Inclusion, Randomization, Blood Sample, and Vaccination

1) Give the subject's parent / guardian information about the study, answer any of her / his questions, obtain written informed consent, and give her / him a signed copy.

2) Obtain significant medical history about the subject.

3) Check vaccination history.

4) Obtain demographic data.

5) Check medications and record reportable medication ongoing at the time of inclusion.

6) Check inclusion and exclusion criteria for eligibility.

7) Conduct a physical examination, including, but not limited to, examination of the head (ear, nose, and throat), neck, heart, lungs, abdomen, and extremities. If a routine examination had been performed within the past week by a qualified health care provider, it does not need to be repeated unless there were changes in health status, in which case it may be limited to the affected area.

8) Take the subject's temperature. If the temperature is ≥ 38.0°C / ≥ 100.4°F, postpone vaccination until the condition is resolved.

9) If the subject is eligible, contact the IRT for randomization, to obtain a subject number, and vaccine allocation.

10) Administer the following study vaccines. Each vaccine should be administered in an assigned location (see Operating Guidelines) and documented appropriately:

Table 5.3: Vaccinations and route of administration at V01, V02, and V03

Vaccine		Route of administration
SP0202 or Prevnar 13	Observer-blind but double-blind across SP0202	Inject IM into the anterolateral area of the thigh, preferably the right thigh
Pentacel	Open-label	Inject IM into the anterolateral area of the thigh , preferably the left thigh (ie, the opposite leg from that used for SP0202 or Prevnar)
ENGERIX-B	Open-label	Inject IM into the anterolateral area of the thigh , preferably the left thigh (ie, the opposite leg from that used for SP0202 or Prevnar)
RotaTeq	Open-label	Administer orally per instructions in the package insert

When multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are given in the same limb, the injection sites should be separated by 1 inch / 2.5 cm or more, so that any local reactions can be differentiated (40).

Pentacel and ENGERIX-B (as applicable) should be given in the same thigh. They should not be administered in the same thigh as SP0202 or Prevnar. For details see Operating Guidelines.

Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the vaccination form of the eCRF. If the vaccines are not administered in the recommended limb(s), this should be corrected for subsequent injections.

11) Keep the subject under observation for 30 minutes and report any reaction / event in the source document.

12) Record the date of injection, site of injection, route of administration, as well as the dose number of the vaccine.

13) Give the parent / guardian a DC1 to record any injection site and systemic AEs, together with instructions for its completion, including explanations on the definition and use of intensity scales for collection of AEs. Remind parents to carefully report any clinical signs / diagnosis experienced at the same time as the fever episode > 39.5°C / 103.1°F.

14) Give the parent / guardian a thermometer for rectal temperature measurements, and a ruler to measure the size of any injection site reactions, and go over the instructions for their use.

15) Arrange an appointment for V02 (D60 ± 14 days). Remind the parent / guardian to expect a telephone call 8 days after V01 and to bring back the DC1 when they return for V02 at a specified date and time.

16) Remind the parent / guardian to notify the site in case of a serious medical event occurs.

17) Complete the source document and relevant CRFs for this visit.

Telephone Call 1 (8 [+2] days after Visit 1)

Note: If D8 falls on a weekend or a holiday, the telephone call may be made on the following business day.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Remind the parent / guardian to do the following:
   - Complete the Day 0–7 pages of the DC1
   - Complete the remaining pages of the DC1, and bring them to V02
   - Notify the site in case of an SAE

Visit 2 (60 [±14] days after Visit 1): Collection of Safety Information and Vaccination

1) If the DC1 information from Day 0–7 has not yet been obtained, obtain it at this time by interviewing the parents. Review the pages of the DC1 with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination.
2) Check medications and record reportable ongoing medications.
3) Conduct a physical examination, including, but not limited to, examination of the head (ear, nose, and throat), neck, heart, lungs, abdomen, and extremities. If a routine examination had been performed within the past week by a qualified health care provider, it does not need to be repeated unless there were changes in health status, in which case it may be limited to the affected area.
4) Take the subject's temperature. If the temperature is ≥ 38.0°C / ≥ 100.4°F, postpone vaccination until the condition is resolved.
5) Contact IRT system for vaccine allocation.
6) Inject the following study vaccines. Each vaccine should be administered in an assigned location (see Operating Guidelines) and documented appropriately. Refer to Table 5.3 for details on vaccinations and route of administration at V01, V02, and V03.

   When multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are given in the same limb, the injection sites should be separated by 1 inch / 2.5 cm or more, so that any local reactions can be differentiated (40).

   Pentacel and ENGERIX-B (as applicable) should be given in the same thigh. They should not be administered in the same thigh as SP0202 or Prevnar. For details see Operating Guidelines.

   Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the vaccination form of the eCRF. If the vaccines are not administered in the recommended limb(s), this should be corrected for subsequent injections.

7) Keep the subject under observation for 30 minutes and record any adverse reaction in the source document.
8) Give the parent / guardian a DC2. Remind parents to carefully report any clinical signs / diagnosis experienced at the same time as the fever episode > 39.5°C / 103.1°F.
9) Arrange an appointment for V03 (D120 ± 14 days). Remind the parent / guardian to expect a telephone call 8 days after V02 and to bring back the DC2 when they return for V03 at a specified date and time.
10) Remind the parent / guardian to notify the site in case of a serious medical event occurs.
11) Complete the source document and the relevant CRFs for this visit.

Telephone Call 2 (8 [+2] days after Visit 2)

Note: If D8 falls on a weekend or a holiday, the telephone call may be made on the following business day.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.
2) Remind the parent / guardian to do the following:
   - Complete the Day 0–7 pages of the DC2
   - Complete the remaining pages of the DC2, and bring them to V03
   - Notify the site in case of an SAE

Visit 3 (60 [±14] days after Visit 2): Collection of Safety Information and Vaccination

1) If the DC2 information from Day 0–7 has not yet been obtained obtain it at this time by interviewing the parents. Review the pages of the DC2 with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination.
2) Check medications and record reportable ongoing medications.
3) Conduct a physical examination, including, but not limited to, examination of the head (ear, nose, and throat), neck, heart, lungs, abdomen, and extremities. If a routine examination had been performed within the past week by a qualified health care provider, it does not need to be repeated unless there were changes in health status, in which case it may be limited to the affected area.
4) Take the subject's temperature. If the temperature is ≥ 38.0°C / ≥ 100.4°F, postpone vaccination until the condition is resolved.
5) Contact IRT system for vaccine allocation.

6) Inject the following study vaccines. Each vaccine should be administered in an assigned location (see Operating Guidelines) and documented appropriately. Refer to Table 5.3 for details on vaccinations and route of administration at V01, V02, and V03.

   When multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are given in the same limb, the injection sites should be separated by 1 inch / 2.5 cm or more, so that any local reactions can be differentiated (40).

   Pentacel and ENGERIX-B (as applicable) should be given in the same thigh. They should not be administered in the same thigh as SP0202 or Prevnar. For details see Operating Guidelines.

   Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the vaccination form of the eCRF. If the vaccines are not administered in the recommended limb(s), this should be corrected for subsequent injections.

7) Keep the subject under observation for 30 minutes and record any adverse reaction in the source document.

8) Give the parent / guardian a DC3. Remind parents to carefully report any clinical signs / diagnosis experienced at the same time as the fever episode > 39.5°C / 103.1°F.

9) Arrange an appointment for V04 (D150 + 14 days). Remind the parent / guardian to expect a telephone call 8 days after V03 and to bring back the DC3 when they return for V04 at a specified date and time.

10) Remind the parent / guardian to notify the site in case of a serious medical event occurs.

11) Complete the source document and the relevant CRFs for this visit.

Telephone Call 3 (8 [+2] days after Visit 3)

Note: If D8 falls on a weekend or a holiday, the telephone call may be made on the following business day.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.

2) Remind the parent / guardian to do the following:

   - Complete the Day 0–7 pages of the DC3
   - Complete the remaining pages of the DC3, and bring them to V04
   - Notify the site in case of an SAE

Visit 4 (30 [+14] days after Visit 3): Collection of Safety Information and Blood Sample

1) If the DC3 information from Day 0–7 has not yet been obtained, obtain it at this time by interviewing the parents. Review the pages of the DC3 / eDC3 with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination.

2) Check medications and record reportable ongoing medications. Review temporary contraindications for blood sampling. Ensure the subject has not had any antibiotics within the previous 72 hours (3 days).
3) Conduct a physical examination and take subject's temperature if necessary, based on the health status of the subject.
4) Obtain the blood sample (BL0002 – 6 mL) (see Section 7.1 for detailed instructions regarding the handling of blood samples).

   If the blood sample cannot be obtained, the parent/guardian should be given the opportunity to bring the subject back to the study site for another attempt, as long as the subject continues to remain eligible for the study. All attempts should be made to obtain a blood sample; however, if the attempts are unsuccessful, the subject could continue in the study with all the study procedures including vaccination.
5) Give the parent / guardian a DC4.
6) Arrange an appointment for V05 (D300–390 ± 14 days). Remind the parent / guardian to bring back the DC4 when they return for V05 at a specified date and time.
7) Complete the end of study phase CRF of the CRB.
8) Complete the source document and the relevant CRFs for this visit.

Visit 5 (180 [±14] days after Visit 3): Collection of Safety Information, Blood Sample, and Vaccination

Note: V05 can take place up from the day subject turns to 12 months until 15 months of age[a].

1) If the DC4 information from Day 0–7 has not yet been obtained, obtain it at this time by interviewing parents. Collet and review the pages of the DC4 with the parent / guardian.
2) Obtain significant medical history about the subject.
3) Check medications and record reportable ongoing medications. Review temporary contraindications for blood sampling. Ensure the subject has not had any antibiotics within the previous 72 hours (3 days).
4) Conduct a physical examination, including, but not limited to, examination of the head (ear, nose, and throat), neck, heart, lungs, abdomen, and extremities. If a routine examination had been performed within the past week by a qualified health care provider, it does not need to be repeated unless there were changes in health status, in which case it may be limited to the affected area.
5) Take the subject's temperature. If the temperature is ≥ 38.0°C / ≥ 100.4°F, postpone vaccination until the condition is resolved.
6) Contact IRT system for vaccine allocation.

[a] "15 months" means the day before the 16th after birth

7) Obtain the blood sample (BL0003 – 6 mL) (see Section 7.1 for detailed instructions regarding the handling of blood samples).

   If the blood sample cannot be obtained, the parent/guardian should be given the opportunity to bring the subject back to the study site for another attempt, as long as the subject continues to remain eligible for the study. All attempts should be made to obtain a blood sample; however, if the attempts are unsuccessful, the subject could continue in the study with all the study procedures including vaccination.

8) Inject the following study vaccines. Each vaccine should be administered in an assigned location (see Operating Guidelines) and documented appropriately:

Table 5.4: Vaccinations and route of administration at V05

Vaccine		Route of administration
SP0202 or Prevnar 13	Observer-blind but double-blind across SP0202	Inject IM into the anterolateral area of the thigh, preferably the right thigh
M-M-R$_{II}$	Open-label	Inject SC into the anterolateral area of the thigh (preferably the left thigh, ie, the opposite thigh from that used for SP0202 or Prevnar 13) or the outer aspect of the upper left arm
VARIVAX	Open-label	Inject SC into the anterolateral area of the thigh (preferably the left thigh, ie, the opposite thigh from that used for SP0202 or Prevnar 13) or the outer aspect of the upper right arm (ie, the opposite arm from that used for M-M-R$_{II}$)

   When multiple vaccines are administered at a single visit, each vaccine should be administered at a different anatomic site. If vaccines are given in the same limb, the injection sites should be separated by 1 inch / 2.5 cm or more, so that any local reactions can be differentiated (40).

   Failure to administer vaccines in the designated limb will not constitute a protocol deviation, but should be recorded as a comment in the vaccination form of the eCRF.

9) Keep the subject under observation for 30 minutes and record any adverse reaction in the source document.

10) Give the parent / guardian a DC5. Remind parents to carefully report any clinical signs / diagnosis experienced at the same time as the fever episode > 39.5°C / 103.1°F.

11) Arrange an appointment for V06 (D330-420 + 14 days). Remind the parent / guardian to expect a telephone call 8 days after V05 and to bring back the DC5 when they return for V06 at a specified date and time.

12) Remind the parent / guardian to notify the site in case of a serious medical event occurs.

13) Complete the source document and the relevant CRFs for this visit.

Telephone Call 4 (8 [+2] days after Visit 5)

Note: If D8 falls on a weekend or a holiday, the telephone call may be made on the following business day.

1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE occurred, follow the instructions in Section 10 for reporting it.

2) Remind the parent / guardian to do the following:
   - Complete the Day 0–7 pages of the DC5
   - Complete the remaining pages of the DC5, and bring them to V06
   - Notify the site in case of an SAE

Visit 6 (30 [+14] days after Visit 5): Collection of Safety Information and Blood Sample

1) If the DC5 information from Day 0–7 has not yet been obtained, obtain it at this time by interviewing the parents. Review the pages of the DC5 with the parent / guardian, including any AEs, medications, or therapy that occurred since vaccination.
2) Check medications and record reportable ongoing medications. Review temporary contraindications for blood sampling. Ensure the subject has not had any antibiotics within the previous 72 hours (3 days).
3) Conduct a physical examination and take subject's temperature if necessary, based on the health status of the subject.
4) Obtain the blood sample (BL0004 – 6 mL) (see Section 7.1 for detailed instructions regarding the handling of blood samples).
5) Record the study termination.
6) Complete the source document and the relevant CRFs for this visit.
7) Complete the end of study CRF of the CRB.
8) Provide the memory aid (MA) to the subject's parent / guardian

Safety Follow-up Telephone Call (D 480 - 570 + 14 days)

The investigator or authorized designee will:

1) Ask the parent / guardian if the subject has experienced any SAE or AESI in the time since vaccination
2) Complete the relevant CRF for this phone contact.

A follow-up visit can be arranged depending on the information recorded during the phone call.

Follow-up of subjects with Related AEs or with AEs That Led to Study/Vaccination Discontinuation:

Unless a subject or subject's parent/guardian refuses further contact, each subject who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the subject's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the product administered.
- The AE caused the discontinuation of the subject from the study or from vaccination.

5.1.5 Planned Study Calendar

The following dates are approximate. The actual dates may differ as, for example, the study will not start until all the appropriate regulatory and ethical approvals have been obtained.

Planned study period - FVFS (first visit, first subject) to LCLS (last contact, last subject):

- Toddlers: May 2020 to September 2021
- Infants: April 2021 to May 2023

Planned inclusion period - FVFS to FVLS (first visit, last subject):

- Toddlers: May 2020 to March 2021
- Infants: April 2021 to November 2021

Planned vaccination period for toddlers: May 2020 to March 2021

Planned primary vaccination period (V01-V02-V03) for infants: April 2021 to March 2022

Planned booster vaccination period for infants: February 2022 to December 2022

Planned end of study: June 2023

Planned date of final clinical study report: Q4 2023

5.1.6 Early Safety Data Review

The safety of investigational products will be continuously monitored by the Sponsor. An ESDR will be performed, the goal of which is to allow for a cautious, stepwise approach to vaccine administration. [redacted]

The safety data collected will be entered into the CRB and summarized by the Sponsor. A blinded review will be performed by the SMT meetings. An unblinded review by the independent DMC will also be conducted. It is understood that this review is based on preliminary data that have not been subject to validation and database lock. The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined early interim safety analysis will continue unchanged.

The following safety parameters will be assessed as part of the ESDR:

- Immediate unsolicited systemic AEs
- Solicited injection site and systemic reactions
- Unsolicited AEs reported as related by the Investigator
- SAEs
- AESIs

Enrollment of infants will not begin until the end of the review. In addition, the data will be examined for the following:

- Any deaths, regardless of causality
- Any vaccine-related SAEs
- AESIs
- Any signs of injection site necrosis or exfoliative dermatitis
- Grade 3 fever reported in more than 10% of subjects; presence of concurrent infectious disease will be documented.

If any of the above criteria are met, a decision based on the SMT and DMC recommendations will be made as to whether enrollment of infants will be allowed to begin or whether any adjustments ought to be done (eg, an SP0202 formulation should not enter Stage II of the study).

The DMC will review the unblinded data by group to be able to identify any trend for differences between each SP0202 formulation and Prevnar 13 for each safety criterion and overall safety profile. The DMC may recommend removing 1 or more SP0202 formulation from Stage II.

Moreover, the option of partial or full unblinding can be available to the Sponsor through an independent statistician, if required, for a further in-depth review of the data.

The Sponsor's SMT is empowered to recommend a pause in recruitment while it investigates any potential signal or concern. The clinical team and SMT will review the data being generated from the study at regular intervals for any new safety signals or safety concerns.

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

Before the start of the study, the Investigator and / or study staff will determine the recruitment strategy to be used for this study (eg, advertising, database, direct mail, word of mouth referral). Using the relevant methods they will contact an appropriate pool of potential parents / guardians and invite them to participate in the study. The site will ensure that any advertisements or materials used to recruit subjects (eg, letters, pamphlets, posters, etc.) have been submitted to Sanofi Pasteur for review prior to submission to the IEC/IRB for approval.

In addition, a parent / guardian who brings a child to the study site for a routine visit will be invited to enroll the subject in the study, if eligible. Subjects may also be recruited from the general population.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject's parent(s) / guardian voluntarily confirms his or her willingness to allow the child to participate in a particular study. Informed consent must be obtained before any study procedures are performed. The process is documented by means of a written, signed, and dated ICF.

In accordance with GCP, prior to signing and dating the consent form, the subject 's parents / guardian must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.

If new information becomes available that may be relevant to the subject's parent / guardian's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

ICFs will be provided in duplicate, or a photocopy of the signed consent will be made. The original will be kept by the Investigator, and the copy will be kept by the subject's parent / guardian.

Documentation of the consent process should be recorded in the source documents.

5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

5.2.4 Inclusion Criteria

An individual must fulfill *all* of the following criteria to be eligible for study enrollment:

Toddlers and infants

1) Informed consent form has been signed and dated by the parent(s) or other guardian, and by an independent witness, if required by local regulations
2) Subject and parent/guardian are able to attend all scheduled visits and to comply with all study procedures
3) Born at full term of pregnancy (≥ 37 weeks) and/or with a birth weight ≥ 5.5 lbs or 2.5 kg
4) Healthy toddlers / infants as determined by medical history, physical examination, and judgment of the Investigator

Specifically for toddlers

5) Aged 12 to 15 months on the day of the first study visit[a]
6) Subject has received 3 doses of Prevnar 13 and 3 doses of diphteria, tetanus, acellular pertussis, poliovirus and *Haemophilus influenzae* type b antigens in infancy

Specifically for infants

7) Aged 42 to 89 days on the day of the first study visit[b]

5.2.5 Exclusion Criteria

An individual fulfilling *any* of the following criteria is to be excluded from study enrollment:

Toddlers and infants

1) Participation at the time of study enrollment (or in the 4 weeks preceding the first study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure
2) Family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated
3) Blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems
4) Active tuberculosis
5) History of *S. pneumoniae* infection or disease, confirmed either serologically or microbiologically
6) History of any neurologic disorder, including any seizures and progressive neurologic disorders
7) History of Guillain-Barré syndrome
8) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances
9) Verbal report of thrombocytopenia contraindicating intramuscular (IM) vaccination in the Investigator's opinion
10) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination in the Investigator's opinion
11) Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
12) Chronic illness (including, but not limited to, cardiac disorders, congenital heart disease, chronic lung disease, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and know congenital or genetic diseases) that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion

[a] "12 to 15 months" means from the 12th month after birth to the day before the 16th after birth

[b] "42 to 89 days" means the 42th day after birth to the day before the 90th day after birth

13) Any condition which, in the opinion of the Investigator, might interfere with the evaluation of the study objectives

14) In an emergency setting, or hospitalized involuntarily.

15) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C / ≥ 100.4°F). A prospective subject should not be included in the study until the condition has resolved or until 3 days after the febrile event has resolved

16) Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study

Specifically for toddlers

17) Receipt of any vaccine in the 4 weeks preceding the study vaccination or planned receipt of any vaccine from enrollment through the last blood sampling Visit (Visit 2), except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines

18) Receipt of immune globulins, blood or blood-derived products in the past 3 months

19) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

20) History of diphtheria, tetanus, pertussis, poliomyelitis, and/or *H. influenzae* type b infection or disease

Specifically for infants

21) Receipt of any vaccine in the 4 weeks preceding the study vaccination or planned receipt of any vaccine from enrollment through the last blood sampling Visit (Visit 6), except for influenza vaccination or COVID 19 vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines, and COVID-19 vaccines, as applicable per local recommendations.

22) Receipt of immune globulins, blood or blood-derived products since birth.

23) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth

24) Previous vaccination against *S. pneumoniae*

25) Previous vaccination against the following antigens: diphtheria, tetanus, pertussis, *H. influenzae* type b, poliovirus, rotavirus, measles, mumps, rubella, and varicella

26) Receipt of more than 1 previous dose of hepatitis B vaccine

27) History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, measles, mumps, rubella, varicella, *H. influenzae* type b, and/or rotavirus infection or disease

28) History of intussusception

If the subject has a primary physician who is not the Investigator, the site should contact this physician with the parent / guardian's consent to inform him / her of the subject's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.2.6 Medical History

Prior to enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the subject is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the case report book (CRB). The significant medical history section of the CRB contains a core list of body systems and disorders that could be used to prompt comprehensive reporting, as well as space for the reporting of specific conditions and illnesses.

For each condition, the data collected will be limited to:

- Diagnosis (this is preferable to reporting signs and symptoms)
- Presence or absence of the condition at enrollment

The reporting of signs and symptoms in lieu of a diagnosis is strongly discouraged.

Dates, medications, and body systems are not to be recorded, and the information collected will not be coded. Its purpose is to assist in the later interpretation of safety data collected during the study.

5.2.7 Contraindications for Subsequent Vaccinations

5.2.7.1 Temporary Contraindications

Toddlers

Not applicable.

Infants

Should an infant experiences one of the conditions listed below, the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the Table of Study Procedures.

1) Febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment

2) Receipt of any vaccine (other than the study vaccine[s]) in the 4 weeks preceding the study vaccination or planned receipt of any vaccine from enrollment through the last study Visit in

which SP0202 or Prevnar 13 is injected (V05), except for influenza vaccination or COVID-19 vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines, and COVID-19 vaccines, as applicable per local recommendation.

3) Long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months preceding the study vaccination)

5.2.7.2 Definitive Contraindications

Toddlers

Not applicable.

Infants

Should a subject experience 1 of the conditions listed below, the Investigator will discontinue vaccination:

1) An anaphylactic or other significant allergic reaction to the previous dose of vaccine
2) Receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy
3) Ongoing clinical AE related to the previous study vaccination, and in the Investigator's opinion, contraindicating further vaccination
4) SAE related to the study vaccine following the previous study vaccination

Subjects with a definitive contraindication will continue to be followed up for the study-defined safety and immunogenicity assessments, as applicable.

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

The following AEs constitute absolute contraindications to subsequent vaccinations, according to their respective Product Information. If a subject should experience any of these events during the study, irrespective of causality, that subject is not to receive any additional study vaccines but should continue in the study and be followed up for safety only, as per protocol. Only the vaccine which has a related SAE or a definite contraindication will be stopped wherever it is possible to identify the vaccine that caused the event.

Prevnar

1) Hypersensitivity to the active substances, to any of the excipients, to diphtheria toxoid, or to a previous dose of Prevnar 13

Pentacel

1) Severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel, any ingredient of Pentacel, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or *H. influenzae* type b vaccine
2) Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause
3) Progressive neurologic disorder including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized

ENGERIX-B

1) Severe allergic reaction (eg, anaphylaxis) a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast

RotaTeq

1) Demonstrated history of hypersensitivity to the rotavirus vaccine or any component of the vaccine
2) History of Severe Combined Immunodeficiency Disease (SCID)
3) Episode of intussusception

M-M-R$_{II}$

1) Hypersensitivity to any component of the vaccine, including gelatin
2) Anaphylactic or anaphylactoid reactions to neomycin
3) Febrile respiratory illness or other active febrile infection
4) Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, eg, for Addison's disease
5) Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems
6) Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with acquired immune deficiency syndrome (AIDS) or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states
7) Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated

VARIVAX

1) History of severe allergic reaction to any component of the vaccine (including neomycin and gelatin) or to a previous dose of varicella vaccine
2) History of primary or acquired immunodeficiency states, leukemia, lymphoma or other malignant neoplasms affecting the bone marrow or lymphatic system, AIDS, or other clinical manifestations of infection with HIV

3) Individuals receiving immunosuppressive therapy, including individuals receiving immunosuppressive doses of corticosteroids
4) Any febrile illness or active infection, including untreated tuberculosis

5.2.8 Contraindication for Subsequent blood draw

The following is a temporary contraindication to blood draws for toddlers (BL0002 at V02) and for infants (BL0002 at V04 and BL004 at V06):

1) Receipt of oral or injectable antibiotic therapy within 72 hours prior blood draw.

   Note: If a subject receives oral or injectable antibiotic therapy within 3 days prior to the next blood draw, the Investigator will postpone that blood draw until it has been 3 days since the subject last received oral or injectable antibiotic therapy. Postponement must still be within the timeframe for blood draw. If postponement would result in the sample collection falling outside of this timeframe, the blood sample should be collected without postponement, and it should be documented appropriately (in source documents and CRB) that the sample was taken less than 3 days after stopping antibiotic treatment.

5.2.9 Coronavirus Disease 2019 (COVID-19) Vaccine

Should COVID-19 vaccination campaign be implemented during the course of the study for the pediatric population eligible to participate or participating to the study, applicable country recommendations will be implemented. When possible and unless recommended otherwise, a 2-week interval between any study vaccine dose and the COVID vaccine dose is desirable.

If a COVID-19 vaccine dose is received during one study vaccine solicited reactogenicity period it would not be possible to differentiate systemic reactions between them. Likewise, if the COVID-19 vaccine is received between a study vaccine dose and the collection of blood, it will not be possible (at this point) to rule out an immunogenicity interaction. Therefore, in any of the two situations it is recommended that the subject will be pulled out of the per protocol (PP) population but should continue in the study within the full analysis set (FAS).

The type of COVID-19 vaccine received (including tradename) and the date of its administration(s) should be documented in the concomitant medications CRF.

Wherever possible the site of injection of study vaccines should be in the limb separate from the limb in which COVID-19 vaccine is administered (if it has already been administered). Likewise, and if on the control of the study site, any COVID-19 vaccine scheduled to be received after administration of study vaccines should not be received in the same limb as study vaccines. Where it is not possible to have study vaccines and COVID-19 vaccine administered in separate limbs, a distance of at least 1 inch / 2.5 cm should be maintained between the two administration sites.

5.2.10 Conditions for Withdrawal

Parents / Guardians will be informed that they have the right to withdraw their child from the study at any time. A subject may be withdrawn from the study:

- At the discretion of the Investigator or Sponsor due to safety concerns or significant non-compliance with the protocol (based on the Investigator's judgment), without the subject's permission (withdrawal)
- At the request of the parent / guardian (dropout)

The reason for a withdrawal or dropout should be clearly documented in the source documents and in the CRB.

The Investigator must determine whether voluntary withdrawal is due to safety concerns (in which case, the reason for discontinuation will be noted as "Adverse Event") or for another reason.

Withdrawn subjects will not be replaced.

5.2.11 Lost to Follow-up Procedures

In the case of subjects who fail to return for a follow-up examination, documented reasonable effort (ie, documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the source documents.

5.2.12 Classification of Subjects Who Discontinue the Study

For any subject who discontinues the study prior to completion, the most significant reason for early termination will be checked in the CRB. Reasons are listed below from the most significant to the least significant (refer to the CRF completion instructions for additional details and examples):

Adverse Event	To be used when the subject is permanently terminated from the study because of an AE (including an SAE), as defined in Section 9.1.1.1. This category also applies if the subject experiences a definitive contraindication that is an SAE or AE.
Lost to Follow-up	To be used when the subject cannot be found or contacted in spite of efforts to locate him/her before the date of his/her planned last visit, as outlined in Section 5.2.11. The certified letter was sent by the Investigator and returned unsigned, and the subject or parent/guardian did not give any other news and did not come to any following visit.
Protocol Deviation	To be used: • In case of significant noncompliance with the protocol (eg,, deviation of the Inclusion / Exclusion criteria, non-compliance with time windows, blood sampling or vaccination refusal, missed injection/treatment, or error in the vaccine/treatment administration). • If the subject experiences a definitive contraindication that is not an SAE or AE. • The subject or the parent/guardian signed the certified letter sent by the Investigator but did not give any other news and did not come to any following visit.
Withdrawal by Parent / Guardian	To be used: • When the subject or parent/guardian indicated unwillingness to continue in the study • When the subject or parent/guardian made the decision to discontinue participation in the study for any personal reason other than an SAE/AE (eg,, subject is relocating, inform consent withdrawal, etc.)

5.2.13 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the study because of an AE or a protocol deviation.

For subjects where the reason for early termination was lost to follow-up or if the subject withdrew informed consent and specified that they do not want to be contacted again and it is documented in the source document, the site will not attempt to obtain further safety information.

If the subject's status at the end of the study is "Withdrawal by Parent / Guardian", the site will attempt to contact them for the 6-month follow-up except if they specified that they do not want to be contacted again and it is documented in the source document.

5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on how to address any study related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the

appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

This process does not replace the need to report an SAE. The Investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department (please refer to Section 10).

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.4.

5.4 Modification of the Study and Protocol

Any amendments to this study plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments (eg, those that affect the conduct of the study or the safety of subjects) require IEC / IRB approval, and must also be forwarded to regulatory authorities.

An administrative / non-substantial amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. The IECs / IRBs will be notified by the Sponsor if such an administrative / non-substantial amendment is made.

The Investigator is responsible for ensuring that changes to an approved study, during the period for which IEC / IRB approval has already been given, are not initiated without IEC / IRB review and approval, except to eliminate apparent immediate hazards to subjects.

5.5 Interruption of the Study

The study may be discontinued as per ESDR decision or if new data about the investigational product resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the Investigators, the IECs/IRBs, or the governing regulatory authorities in the countries where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by applicable regulatory requirements. The Investigator shall promptly inform the study subjects' parents/guardians and should assure appropriate subject therapy and/or follow-up.

6 Products Administered

6.1 Identity of the Investigational Products

6.1.1 Identity of Study Product 1

SP0202-IIb: Pneumococcal Conjugate Vaccine ([PCV], SK bioscience Co., Ltd.)

Form: Liquid

Dose: 0.5 mL

Route: IM

Batch Number: TBD

6.1.1.1 Composition

Each 0.5 mL dose of vaccine contains the following components:

Active ingredients

6.1.1.2 Preparation and Administration

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor.

The product is a liquid preparation that does not require diluting. Since this product is a suspension containing an adjuvant, white particulate matter and transparent supernatant may be observed during storage of the product; it has to be shaken vigorously immediately prior to use to obtain a homogenous, white suspension. Do not use the vaccine if it cannot be resuspended.

The vaccine is to be administered intramuscularly into the anterolateral aspect of the thigh in infants and toddlers in a volume of 0.5 mL.

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.1.1.3 Dose Selection and Timing

Subjects in Group 1 (toddlers) will receive one dose of PCV, formulation SP0202-IIb, at D0 (V01).

Subjects in Group 5 (infants) will receive one dose of PCV, formulation SP0202- IIb, at D0 (V01), D60 (V02), D120 (V03), and D300-390 (V05).

6.1.2 Identity of Study Product 2

SP0202-VI: Pneumococcal Conjugate Vaccine ([PCV], SK bioscience Co., Ltd.)

Form: Liquid

Dose: 0.5 mL

Route: IM

Batch Number: TBD

6.1.2.1 Composition

Each 0.5 mL dose of vaccine contains the following components:

Active ingredients

[redacted]

6.1.2.2 Preparation and Administration

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.1.2.3 Dose Selection and Timing

Subjects in Group 2 (toddlers) will receive one dose of PCV, formulation SP0202-VI, at D0 (V01).

Subjects in Group 6 (infants) will receive one dose of PCV, formulation SP0202-VI, at D0 (V01), D60 (V02), D120 (V03), and D300-390 (V05).

6.1.3 Identity of Study Product 3

SP0202-VII: Pneumococcal Conjugate Vaccine ([PCV], SK bioscience Co., Ltd.)

Form: Liquid

Dose: 0.5 mL

Route: IM

Batch Number: TBD

6.1.3.1 Composition

Each 0.5 mL dose of vaccine contains the following components:

Active ingredients

[redacted]

6.1.3.2 Preparation and Administration

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.1.3.3 Dose Selection and Timing

Subjects in Group 3 (toddlers) will receive one dose of PCV, formulation SP0202-VII, at D0 (V01).

Subjects in Group 7 (infants) will receive one dose of PCV, formulation SP0202- VII, at D0 (V01), D60 (V02), D120 (V03), and D300-390 (V05).

6.1.4 Identity of Control Product

Prevnar 13: Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc, Philadelphia, PA, USA)

Form: Liquid

Dose: 0.5 mL

Route: IM

Batch Number: Commercial Lot

6.1.4.1 Composition

Each 0.5 mL dose of vaccine contains the following components:

Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides	approximately 2.2 µg of each
6B saccharides	4.4 µg
CRM_{197} carrier protein	34 µg
Polysorbate 80	100 µg
Succinate buffer	295 µg
Aluminum as aluminum phosphate adjuvant	125 µg

6.1.4.2 Preparation and Administration

Prevnar 13 is supplied in a single-dose prefilled syringe.

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.1.4.3 Dose Selection and Timing

Subjects in Group 4 (toddlers) will receive one dose of Prevnar 13, at D0.

Subjects in Group 8 (infants) will receive one dose of Prevnar 13, at D0 (V01), D60 (V02), D120 (V03), and D300-390 (V05).

6.2 Identity of Other Products

6.2.1 Identity of Other Product 1

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

Form: Liquid

Dose: 0.5 mL

Route: IM

Batch Number: Commercial Lot

6.2.1.1 Composition

Each 0.5 mL dose contains:

Diphtheria toxoid ..... 15 Limit of Flocculation (Lf)
Tetanus toxoid ..... 5 Lf

Acellular pertussis antigens:

Pertussis toxin (PT) ..... 20 µg
Filamentous hemagglutinin (FHA) ..... 20 µg
Pertactin (PRN) ..... 3 µg
Fimbriae Types 2 and 3 (FIM) ..... 5 µg

Inactivated polioviruses:

Type 1 (Mahoney) ..... 40 D-antigen units (DU)
Type 2 (MEF-1) ..... 8 DU
Type 3 (Saukett) ..... 32 DU

H. influenzae type b (PRP) ..... 10 µg
Tetanus toxoid (PRP-T) ..... 24 µg

Excipients:

Aluminum phosphate (0.33 mg aluminum) (adjuvant) ..... 1.5 mg
Polysorbate 80 ..... approximately 10 parts per million (ppm) by calculation
Sucrose ..... 42.5 mg
Residual formaldehyde ..... ≤ 5 µg
Residual glutaraldehyde ..... < 50 ng
Residual bovine serum albumin ..... ≤ 50ng
2-phenoxyethanol ..... 3.3 mg (0.6% v/v)
Neomycin ..... < 4 picogram (pg)
Polymyxin B sulfate ..... < 4 pg

6.2.1.2 Preparation and Administration

The general precautions of use are the same as those described for the study product in Section 6.1.1.2

Pentacel will be supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single dose vials.

One dose (0.5 mL) is to be injected in the anterolateral aspect of thigh. After gently swirl the vial, the suspension should be cloudy, uniform and white to off-white (yellow tinge).

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

The procedures for preparing and administering Pentacel are detailed in the package insert (33).

6.2.1.3 Dose Selection and Timing

Subjects in Groups 1, 2, 3, and 4 will receive one dose of Pentacel at D0 (V01).

Subjects in Groups 5, 6, 7, and 8 (infants) will receive one dose of Pentacel at D0 (V01), D60 (V02), and D120 (V03).

6.2.2 Identity of Other Product 2

ENGERIX-B (Hepatitis B Vaccine [Recombinant]); GlaxoSmithKline

Form: Liquid

Dose: 0.5 mL

Route: IM

Batch Number: Commercial Lot

6.2.2.1 Composition

Each 0.5 mL pediatric/adolescent dose contains 10 µg of hepatitis B virus surface antigen (HBsAg) adsorbed on 0.25 mg aluminum as aluminum hydroxide.

Excipients:

Sodium chloride	9 mg/mL
Disodium phosphate dihydrate	0.98 mg/mL
Sodium dihydrogen phosphate dihydrate	0.71 mg/mL

6.2.2.2 Preparation and Administration

The general precautions of use are the same as those described for the study product in Section 6.1.1.2

ENGERIX-B will be supplied as 0.5 mL prefilled syringes.

One dose (0.5 mL) is to be injected in the anterolateral aspect of the thigh for infants. The content, upon storage may present a fine white deposit with a clear colorless supernatant. Once shaken, the vaccine is slightly opaque.

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

The procedures for preparing and administering ENGERIX-B are detailed in the package insert (34).

6.2.2.3 Dose Selection and Timing

Subjects can receive one dose of ENGERIX-B at D0 (V01), D60 (V02), and D120 (V03). Of note, a first dose of hepatitis B vaccine can be given at least 28 days prior to study enrollment.

6.2.3 Identity of Other Product 3

RotaTeq: Rotavirus Vaccine, Live, Oral, Pentavalent (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)

Form: Liquid

Dose: 2 mL

Route: Oral

Batch Number: Commercial Lot

6.2.3.1 Composition

Each 2 mL dose contains the following 5 live reassortant rotaviruses:

G1 serotype..... 2.2 x 10^6 infectious units (IU)
G2 serotype..... 2.8 x 10^6 IU
G3 serotype..... 2.2 x 10^6 IU
G4 serotype..... 2.0 x 10^6 IU
P1A(8) ..... 2.3 x 10^6 IU

The reassortants are suspended in a buffered stabilizer solution.

Each 2 mL vaccine dose also contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum.

6.2.3.2 Preparation and Administration

The general precautions of use are the same as those described for the study product in Section 6.1.1.2

RotaTeq will be supplied in a container consisting of a squeezable plastic dosing tube with a twist-off cap allowing for direct oral administration.

One dose (2 mL) of RotaTeq is to be administered by gently squeezing liquid into infant's mouth toward the inner cheek until dosing tube is empty. A residual drop may remain in the tip of the tube.

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

The procedures for preparing and administering RotaTeq are detailed in the package insert (35).

6.2.3.3 Dose Selection and Timing

Subjects in Groups 5, 6, 7 and 8 (infants) will receive one dose of RotaTeq at D0 (V01), D60 (V02), and D120 (V03).

6.2.4 Identity of Other Product 4

M-M-R$_{II}$: Measles, Mumps, and Rubella Virus Vaccine Live (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)

Form: Liquid

Dose: 0.5 mL

Route: SC

Batch Number: Commercial Lot

6.2.4.1 Composition

Each 0.5 mL dose contains:

Measles virus (derived from Ender's Edmonston strain) propagated in chick embryo cell culture	not less than 1000 $TCID_{50}$*
Mumps virus (Jeryl Lynn™ [B level] strain) propagated in chick embryo cell culture	not less than 12 500 $TCID_{50}$*
Rubella virus (Wistar RA 27/3 strain) propagated in WI-38 human diploid lung fibroblasts	not less than 1000 $TCID_{50}$*

*$TCID_{50}$ = tissue culture infectious doses 50%

Other ingredients

- sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, trace amounts of fetal bovine serum

6.2.4.2 Preparation and Administration

The general precautions of use are the same as those described for the study product in Section 6.1.1.2

M-M-R$_{II}$ will be supplied as a vial of lyophilized vaccine and a vial of diluent for reconstitution to prepare a single dose (0.5 mL).

One dose (0.5 mL) of M-M-R$_{II}$ is to be administered SC in the anterolateral area of the thigh or the outer aspect of the upper arm. The site of injection is to be documented. The site of injection is to be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle are to be disposed of in accordance with currently established guidelines.

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

The procedures for preparing and administering M-M-R$_{II}$ are detailed in the package insert (36).

6.2.4.3 Dose Selection and Timing

Subjects in Groups 5, 6, 7 and 8 (infants) will receive one dose of M-M-R$_{II}$ at D300-390 (V05).

6.2.5 Identity of Other Product 5

VARIVAX: Varicella Virus Vaccine Live (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA)

Form: Liquid

Dose: 0.5 mL

Route: SC

Batch Number: Commercial Lot

6.2.5.1 Composition

Each approximately 0.5 mL dose contains:

Live, attenuated Oka/Merck varicella virus ..... at least 1350 plaque-forming units (PFU)

Excipients:

Sucrose .....25 mg
Hydrolyzed gelatin .....12.5 mg
Sodium chloride.....3.2 mg
Monosodium L-glutamate .....0.5 mg
Sodium phosphate dibasic .....0.45 mg
Potassium phosphate monobasic .....0.08 mg
Potassium chloride.....0.08 mg

The vaccine contains residual components of MRC-5 cells including DNA and protein and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum. The vaccine contains no preservative.

6.2.5.2 Preparation and Administration

The general precautions of use are the same as those described for the study product in Section 6.1.1.2

VARIVAX will be supplied as a vial of lyophilized vaccine and a vial of diluent for reconstitution to prepare a single dose (0.5 mL).

One dose (0.5 mL) of VARIVAX is to be administered SC into the anterolateral area of the thigh or the outer aspect of the upper arm. The site of injection is to be documented. The site of injection will be prepared with a suitable antiseptic. After administration of the vaccine, the used syringe and needle were to be disposed of in accordance with currently established guidelines.

Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRB. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

The procedures for preparing and administering VARIVAX are detailed in the package insert (37).

6.2.5.3 Dose Selection and Timing

Subjects in Groups 5, 6, 7 and 8 (infants) will receive one dose of VARIVAX at D300-390 (V05).

6.3 Product Logistics

6.3.1 Labeling and Packaging

The study products will be dispatch in pre-filled syringes containing 0.5 mL of PCV formulations each. The 3 formulations of the SP0202 PCV are to be labeled and packed in the same way, according to the applicable national regulation. Applicable local regulatory text will be included on the label for each country.

The comparator vaccine (Prevnar 13) will be supplied as per the standard commercial packaging: the syringe will retain the original commercial label and the carton will have a clinical label with a dose number and a detachable label.

Commercial lots of the routine pediatric vaccines (Pentacel, ENGERIX-B, RotaTeq, M-M-RII, and VARIVAX) will be supplied by Sanofi Pasteur, Inc.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

The Clinical Logistics Coordinator or designee will contact the Investigator or a designee to determine the dates and times of delivery of products.

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the Operating Guidelines, including checking that the cold chain was maintained during shipment (ie,, verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should immediately quarantine the product, alert the Sanofi Pasteur representative, and request authorization from Sanofi Pasteur to use the product.

6.3.2.2 Product Storage

The Investigator will be personally responsible for product management or will designate a staff member to assume this responsibility.

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator / freezer at a temperature ranging from:

- +2°C to +8°C for Prevnar 13, SP0202, Pentacel, Hepatitis B, and RotaTeq
- –50°C to +8°C for M-M-R$_{II}$
- –50°C to –15°C or +2°C to + 8°C for VARIVAX (depending on locally approved monograph)

They should be protected from light. All vaccines but M-M-R$_{II}$ and VARIVAX, must not be frozen. The temperature must be monitored and documented (see the Operating Guidelines) for the entire time that the vaccine is at the study site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

6.3.2.3 Product Accountability

As the study is observer-blinded, the “unblinded study personnel” will be in charge of product management at the site and will maintain records of product delivery to the study site, product inventory at the site, the dose given to each subject, and the disposal of or return to the Sponsor of unused doses.

The necessary information on the product labels is to be entered into the source document and the CRB. If applicable, information may also be entered into the subject’s vaccination card.

The Sponsor’s monitoring staff will verify the study site’s product accountability records against the record of administered doses in the CRBs and the communication from the IRT (if applicable).

In case of any expected or potential shortage of product during the study, the Investigator or an authorized designee should alert the Sanofi Pasteur representative as soon as possible, so that a shipment of extra doses can be arranged.

6.3.3 Replacement Doses

If a replacement dose is required (eg, because the syringe broke or particulate matter was observed in the syringe), the unblinded site personnel must either contact the IRT to receive the new dose allocation, or follow the instructions given in the Operating Guidelines.

6.3.4 Disposal of Unused Products

Unused or wasted products will be either disposed of or returned to the Sponsor in accordance with the instructions in the Operating Guidelines. Product accountability will be verified throughout the study period.

6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigator(s) will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

The study will be performed in an observer-blind fashion:

- Investigators and study staff who conduct the safety assessment and the subject will not know which vaccine is administered
- Only the study staff who prepare and administer the vaccine and are not involved with the safety evaluation will know which vaccine is administered

This study will be observer-blinded between any SP0202 formulation and Prevnar 13 and double-blind across the 3 SP0202 formulations.

The subject, the Investigator and study staff members who collect safety data, and laboratory personnel who analyze the blood samples, will not know which products was administered. The vaccinator will be in charge of preparing and administering the products and will not be authorized to collect any safety data. In addition, the vaccinator or authorized designee will have to ensure that the documents on randomization are stored in a secure place where only she / he has access.

It is to be noted that the vaccinator will know whether the injected product is Prevnar 13 or one of the SP0202 formulations. However, she / he will not be able to tell the SP0202 formulations apart.

The code may be broken in the event of an AE only when the identification of the vaccine received could influence the treatment of the subject. Code-breaking should be limited to the subject(s) experiencing the AE.

The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has

been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur RMO if a subject's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code breaking CRF is to be completed.

A request for the code to be broken may also be made:

- By the GPV Department through an internal system for reporting to Health authorities in the case of an SAE as described in ICH E2A. In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (ie, the subject's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.
- By the IDMC if needed to facilitate their assessment of safety.

The IEC / IRB must be notified of the code-breaking. All documentation pertaining to the event must be retained in the site's study records and in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

[redacted] An unblinded independent statistician will share unblinded outputs with the DMC members. The information will not be communicated to either the Investigator or the Sponsor study team before the end of the Stage I and database lock.

The detailed information related to DMC activities, including the planned frequency and scope of the meetings and reviews are described in the charter.

If during the internal SMT review a further in-depth review of the data and partial or full unblinding is required by the Sponsor, it will be done by an independent statistician and communicated to the Sponsor.

[redacted]

6.5 Randomization and Allocation Procedures

On the day of enrollment, subjects who meet the inclusion/exclusion criteria and sign the ICF will be randomly assigned to Groups 1 through 4 in a 1:1:1:1 ratio to have approximatively 140 subjects (35 subjects in each treatment group) for toddlers subjects (Stage I) or to Group 5 through 8 in a 1:1:1:1 ratio to have approximatively 700 subjects (175 subjects in each treatment group) for infants subjects (Stage II). Stage II randomization will be at least stratified by country.

Following DMC assessment, in case one or more of the SP0202 formulations may not be included in the stage II, the randomization list will match with the selected groups for stage II; the sample size of each group will remain unchanged (175 subjects by group) and the ratio between groups will be balanced.

Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will randomize the subjects and then provide the vaccine assignment and have the site staff confirm it. The full detailed procedures for group allocation are described in the Operating Guidelines. If the subject is not eligible to participate in the study, then the information will only be recorded on the subject recruitment log.

IRT will also be used to randomly allocate subject to the OPA subset in Stage II (around 125 infants by group). This allocation has no impact on the study conduct on site; the list of selected subjects will be communicated to the laboratory personnel.

Subject numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit subject identifier). The first digit of the subject identifier will be ‘1’ for toddlers subjects randomized into Stage 1 and ‘2’ for infants subjects randomized into Stage 2. For example, Subject 840000110005 is the fifth toddler subject enrolled in Center Number 1 in the US in stage I (840 being the US country code), and Subject 840000120005 is the fifth infant subject enrolled in Center Number 1 in the US (840 being the US country code).

6.6 Treatment Compliance

The following measures will ensure that the vaccine doses administered comply with those planned, and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified study personnel
- The person in charge of product management at the site will maintain accountability records of product delivery to the study site, product inventory at the site, dose(s) given to each subject, and the disposal of unused or wasted doses

6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications and other therapies (eg, blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during study participation.

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of first vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the day of each vaccination to the end of the solicited and unsolicited follow-up period.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Three standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], steroids/corticosteroids [therapy duration for less than 2 consecutive weeks])

Note: Topical steroids (Inhaled, otic, ophthalmic, nasal etc.) should not be captured or reported.

- Category 2: medications impacting or that may have an impact on the immune response (eg, other vaccines [including influenza vaccine in the 2 weeks [14 days) preceding or following any study vaccination], blood products, antibiotic classes taken within 3 days [72 hours] prior to blood draw that may interfere with bioassays used by the GCI department, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors, immune globulins preceding in the 3 months preceding any vaccination for infants)

Note: Topical antibiotics (Inhaled, otic, ophthalmic, nasal, etc.) should not be captured or reported.

- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, long-term systemic corticosteroid therapy [prednisone or equivalent for more than 2 consecutive weeks])

Note: Topical steroids (Inhaled, otic, ophthalmic, nasal etc.) should not be captured or reported.

The information reported in the CRB for each reported medication will be limited to:

- Trade name for a medication composed of several molecules OR international nonproprietary name (INN) for a medication composed of one single molecule
- Origin of prescription: prophylaxis Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the Action Taken of the AE collection tables.
- Medication category (1, 2, or 3)
- Start and stop dates

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication(s) received belongs to one of the prelisted categories. Medications will not be coded.

7 Management of Samples

Blood samples for the assessment of antibody responses will be collected at V01 and V02 for toddlers; at V01[a], V04, V05, and V06 for infants. See the Table of Study Procedures and Section 5.1.3 for details of the sampling schedule.

7.1 Sample Collection

At Visits that include a blood draw, 6 mL (at V01 and V02 for toddlers and at V04, V05 and V06 for infants) and 3 mL (at V01 for infants[a]) of blood will be collected in tubes provided by or recommended by the Sponsor. Immediately prior to the blood draw, the staff member performing the procedure will verify the subject's identity as well as the assigned subject's number and sampling stage on the pre-printed label, and will attach the label to the tube. When vaccination and blood sample collection occur at the same visit and vaccine is given only in one of the arms, blood is to be taken from the limb opposite to the one that will be used for vaccination, if possible.

Optional blood collection for routine screening tests (not part of study) for the US sites only

The American Academy of Pediatrics (AAP) recommends blood lead screening as part of routine health supervision for children at 9 to 12 MoA and, if possible, again at 24 months of age. Further, the AAP recommends universal screening for anemia at approximately 12 MoA with determination of hemoglobin concentration and an assessment of risk factors associated with iron deficiency and iron deficient anemia (41). Children enrolled in this study will undergo routine screening outside of the study. Collection of blood for lead and anemia screening could be done at the same time as blood is drawn for the study immunologic assessment via the same venipuncture. This collection should be done in sample tubes which are not part of the study, and as per standard

[a] Not applicable from protocol Version 5.0

of care. The results of these tests will not be part of the study report. Blood collection for these screening tests could be done at any visit in the 2nd year of life, once for complete blood count (CBC) (1 mL) and twice for lead blood levels (2 mL for each test).

7.2 Sample Preparation

Detailed instructions on how to prepare blood samples for assessment of immune response are contained in the Operating Guidelines provided to the site. An overview of the procedures is provided here.

[redacted]

7.3 Sample Storage and Shipment

During storage, serum tubes are to be kept in a freezer whose temperature is set and maintained at -20°C or below. The temperature will be monitored and documented on the appropriate form during the entire study. If it rises above -10°C for any period of time, the Clinical Logistics Coordinator must be notified. See the Operating Guidelines for further details.

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the Clinical Logistics Coordinator. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the United Nations (UN) Class 6.2 specifications and the International Air Transport Association (IATA) 602 packaging instructions.

Samples will be shipped to Global Clinical Immunology (GCI) at Sanofi Pasteur. The address is provided in the Operating Guidelines.

Blood samples will be aliquoted at GCI. [redacted]

7.4 Future Use of Stored Biological Samples for Research

Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) for up to 25 years after the end of the study. These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

In addition, Subjects' parents / guardians will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

8 Clinical Supplies

Sanofi Pasteur will supply the study sites with protocols, ICFs, CRBs, SAE reporting forms, DCs/eDCs, MAs/eMAs, and other study documents, as well as with the following study materials: all study vaccines, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

The means for performing Electronic Data Capture (EDC) will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the study.

The Investigator will supply all vaccination supplies, phlebotomy, and centrifugation equipment, including biohazard and / or safety supplies. The biohazard and safety supplies include needles and syringes, examination gloves, laboratory coats, sharps disposal containers, and absorbent countertop paper. The site will ensure that all biohazard wastes are autoclaved and disposed of in accordance with local practices. The Investigator will also supply appropriate space in a temperature-monitored refrigerator for the storage of the products and for the blood samples, and appropriate space in a temperature-monitored freezer for serum aliquots.

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the Operating Guidelines.

9 Endpoints and Assessment Methods

9.1 Primary Endpoints and Assessment Methods

9.1.1 Safety

9.1.1.1 Safety Definitions

The following definitions are taken from the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Adverse Event (AE):

An AE is any untoward medical occurrence in a patient or in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore an AE may be:

- A new illness
- The worsening of a pre-existing condition
- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

Surgical procedures are not AEs; they are the actions taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the study period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing medical condition worsens following study interventions in frequency or intensity, or if according to the Investigator there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (eg, asthma) if the frequency or intensity increases post-vaccination.

Serious Adverse Event (SAE):

Serious and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on subject / event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death

- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability / incapacity[c]
- Is a congenital anomaly / birth defect
- Is an important medical event (IME)

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as IMEs that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These IMEs should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new onset diabetes, or autoimmune disease.

Adverse Reaction:

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse reactions (AR).

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility)

The following additional definitions are used by Sanofi Pasteur:

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs (including those related to the product administered) that occur within the first 30 minutes after vaccination.

Solicited Reaction:

A solicited reaction is an "expected" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) prelisted in the protocol and CRB (eg, injection site pain or headache occurring between D0 and D7 post-vaccination).

By definition, solicited reactions are to be considered as being related to the product administered.

For injectable vaccines, solicited reactions can either be solicited injection site reactions or solicited systemic reactions.

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[a] The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: hospitalization planned before inclusion into the study or outpatient treatment with no hospitalization.

[c] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

Unsolicited AE / AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of diagnosis and/or onset window post-vaccination. For example, if headache between D0 and D7 is a solicited reaction (ie, prelisted in the protocol and CRB), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

Injection Site Reaction:

An injection site reaction is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions. They are considered to be related to the product administered.

Systemic AE:

Systemic AEs are all AEs that are not injection or administration site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Adverse Event of Special Interest (AESI):

An adverse event of special interest is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg,, regulators) might also be warranted.

9.1.1.2 Safety Endpoints

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 subject'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

Other endpoints will be recorded or derived as described in the statistical analysis plan. Depending on the item, these could include: nature (Medical Dictionary for Regulatory Activity [MedDRA] preferred term), time of onset, duration, number of days of occurrence, Grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.

9.1.1.3 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.

9.1.1.3.1 Immediate Post-vaccination Observation Period

Subjects 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 Section 10.

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

After each vaccination, subjects 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 subjects 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

Subjects' 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 9.1 and Table 9.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the DC / eDC, and CRB, together with the intensity scales.

Table 9.1: 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 9.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	Fever	Vomiting	Crying abnormal	Drowsiness	Appetite lost	Irritability
Electronic 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.

9.1.1.3.3 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 subject 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.
See Section 10 for further details on SAE reporting.

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 9.1 and Table 9.2).

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

[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 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.

- 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", as described in Section 9.1.1.3.5.

- 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

9.1.1.3.4 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 (42)
- 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 Section 10. Further instructions on the data collection for this event and the relevant definition will be provided in the Operating Guidelines.

9.1.1.3.5 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 subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

9.1.2 Immunogenicity

9.1.2.1 Immunogenicity Endpoints

The primary endpoint(s) 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 subjects 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[a], PD3, before Dose 4, and at PD4
- Serotype specific IgG concentrations ratios (PD3/pre-dose 1[a] and PD4/pre-dose 4) for each pneumococcal serotype included in the SP0202 formulations, as measured by ECL

9.1.2.2 Immunogenicity Assessment Methods

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

This method will be performed on BL0001 and BL0002 collected from toddlers, and on BL0001[a], BL0002, BL0003, and BL0004 collected from infants (See Table 9.3 and Table 9.4).

9.1.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Safety

There are no secondary objectives for safety.

[a] Not applicable from protocol Version 5.0

9.2.2 Immunogenicity

9.2.2.1 Immunogenicity Endpoints

9.2.2.1.1 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 subjects 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 subjects 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

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

Toddlers

Before vaccination (D0) in all subjects:

- 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 subjects:

- 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 subjects (D0)[a]:

- Anti-rotavirus serum immunoglobulin (Ig) A 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 subjects:

- 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[a]
- 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

[a] Not applicable from protocol Version 5.0

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

- Anti-measles Ab concentrations
- 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

9.2.2.2 Immunogenicity Assessment Methods

A summary of the tests conducted per time point for toddlers and for infants is provided in Table 9.3 and in Table 9.4, respectively. This also includes test carried out for primary endpoints (ie, PnPS-ECL).

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

Table 9.3: 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 9.4: 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

* Not applicable from protocol Version 5.0

Multiplexed opsonophagocytic killing assay (MOPA)

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

[redacted]

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

The assay for measuring anti-HB antibodies will be performed at GCI, Sanofi Pasteur, Swiftwater, PA, USA.

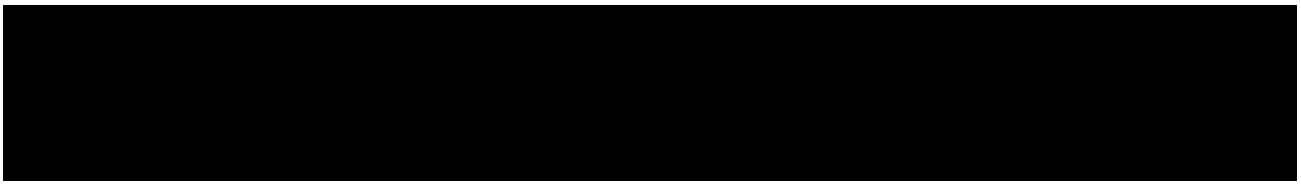
[redacted]

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.

9.2.3 Efficacy

No clinical efficacy data will be obtained in the study.

9.3 Observational Endpoints and Assessment Methods

There are no observational objectives in this study.

10 Reporting of Serious Adverse Events

To comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship, and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational product(s). It is the responsibility of the Investigator to request all necessary documentation (eg, medical records, discharge summary) in order to provide comprehensive safety information. All relevant information must then be transcribed onto the AE CRF and the appropriate Safety Complementary Information CRFs.

10.1 Initial Reporting by the Investigator

Serious adverse events occurring during a subject's participation in the study or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The Investigator (licensed physician [M.D. or D.O.]) must validate the information entered on the AE CRF by completing the Investigator validation form.

The Investigator must indicate on the AE CRF that the event was serious and must complete the relevant SAE section of this form as well as the appropriate Safety Complementary Information CRFs. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA, and the RMO with relevant SAE information details.

If the EDC system is unavailable, the site must notify the Sponsor, using the paper version of the CRB, as described in the operating guidelines.

The Investigator must complete the paper copies of the AE CRF and of the appropriate Safety Complementary Information CRFs and send them to the Sponsor by <one of> the following means:

- By fax, to the following number: 570-957-2782
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofipasteur.com

- By express mail, to the following address:

  Sanofi Pasteur Inc.
  Reception and Triage – Case Management
  Global PharmacoVigilance
  Mail Drop: 45D38
  Discovery Drive
  Swiftwater, PA 18370

When the EDC system becomes available, the Investigator must transcribe the information from the paper forms into the EDC system.

If there is need for urgent consultation, the Investigator is to contact the RMO. If the RMO cannot be reached, the Investigator may contact the Call Center as described in Section 5.3.

10.2 Follow-up Reporting by the Investigator

The AE CRF completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (eg, outcome, precise description of medical history, results of the investigation). All relevant information must be included directly in the AE CRF and the appropriate Safety Complementary Information CRFs. An e-mail alert will be sent automatically to the GPV Department and to the CRA. Copies of documents (eg, medical records, discharge summary, autopsy) may be requested by the GPV Department.

The anonymity of the subject must always be respected when forwarding this information.

10.3 Reporting of SAEs Occurring After a Subject Has Completed the Study

Any SAE that occurs after a subject has completed the study but that is likely to be related to the investigational product(s), other products (eg, a benefit vaccine), or to the experiment must also be reported as soon as possible. In such a case, the reporting procedure to be followed is identical to that described in Section 10.1.

10.4 Assessment of Causality

The causal relationship between the SAE and the investigational product administered will be evaluated by the Investigator as described in Section 9.1.1.3.5.

Following this, the Sponsor's Global Safety Officer will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The causal relationship to study procedures will be also assessed in the CRB.

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Investigator(s).

10.5 Reporting SAEs to Health Authorities and IECs / IRBs

The Sponsor will inform the relevant health authorities of any reportable SAEs according to the local regulatory requirements. Reporting to the health authorities will be according to the Sponsor's standard operating procedures.

The Sponsor will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators will be responsible for informing the IECs or IRBs that reviewed the study protocol.

11 Data Collection and Management

11.1 Data Collection and CRB Completion

Individual DCs/eDCs, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information as described in Section 9.1.1.3. These DCs/eDCs will include prelisted terms and intensity scales (see Table 9.1 and Table 9.2) as well as areas for free text to capture additional safety information or other relevant details. Parents or guardians will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct parents / guardians on how to correctly use these tools.

The 6-month follow-up will be done by interviewing subjects' parent / guardian either during a visit or over the telephone using a questionnaire to capture SAEs and AESIs, if applicable. A memory aid may be provided to the subjects' parent / guardian at the preceding visit to help them record information on events occurring between this visit and the 6-month follow-up.

Relevant information will be transcribed into the AE CRF. Any SAEs captured during the 6-month follow-up period will be reported and followed-up as per the normal process for reporting SAEs.

At specified intervals, the Investigator or an authorized designee will interview the parents / guardians to collect the information recorded in the DC / eDC, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRB. (Any information that was not documented in the DC / eDC will first be captured in the source document and then reported electronically.) The CRB has been designed specifically for this study under the responsibility of the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the CRBs, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to all site staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion instructions will be provided to assist with data entry during the course of the study.

Upon completion of training, each user requiring access to the EDC system will be issued a unique username and password. In the event of a change in study personnel, each newly assigned individual will receive a unique username and password; the username and password of a previous user may not be reissued. If any study personnel leave the study, the Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be initiated in the EDC system at the time of the first data entry to track all modifications and ensure database integrity.

The Investigator is responsible for the timeliness, completeness, and accuracy of the information in the CRBs; must provide explanations for all missing information; and must sign the CRB using an e-signature.

11.2 Data Management

Management of SAE Data

During the study, SAE data (reported on the AE, Death, and Safety Complementary Information CRFs) will be integrated into the Sponsor's centralized GPV database upon receipt of these forms and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the Global Safety Officer and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

The information from the GPV database cases will be reconciled with that in the clinical database.

Management of Clinical and Laboratory Data

Clinical data, defined as all data reported in the CRB, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.

During the study, clinical data reported in the CRBs will be integrated into the clinical database under the responsibility of the Sanofi Pasteur CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and / or consistency checks will be systematically applied to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the study. Any questions pertaining to the reported clinical data will be submitted to the Investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

The validation of the immunogenicity data will be performed at the laboratory level following the laboratory's procedures. Information from the laboratory will be checked for consistency before integration into the clinical Datawarehouse.

After integration of all corrections in the complete set of data, and after the SAE information available from CDM and the GPV Department has been reconciled, the database will be released for statistical analysis.

11.3 Data Review

The safety of investigational products will be continuously monitored by the Sponsor. An ESDR will be performed, the goal of which is to allow for a cautious, stepwise approach to vaccine administration prior to proceeding to Stage II. [redacted]

A blinded review of the data is anticipated through the data review process led by Data Management before database lock.

12 Statistical Methods and Determination of Sample Size

12.1 Statistical Methods

For immunogenicity data, assuming that log10 transformation of the titers / concentrations and titers / concentrations ratio follows a normal distribution, first, the mean and 95% confidence intervals (CIs) will be calculated on log10 (titers / concentrations; titers / concentrations ratio) using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations, to compute geometric mean titers / concentrations (GMTs / GMCs) and geometric mean of the individual titer / concentration ratios (GMTRs / GMCRs) and their 95% CIs.

The 95% CIs of point estimates will be calculated using the exact binomial distribution (Clopper-Pearson method (43)) for proportions.

12.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

12.1.1.1 Hypotheses

All analyses will be descriptive; no hypothesis will be tested.

12.1.1.2 Statistical Methods

Safety

Safety results will be analyzed for subjects 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, time to onset, intensity (Grade 1, Grade 2, or Grade 3), number of days of occurrence and action taken

- Unsolicited AEs occurring within 30 days after injection by system organ class (SOC) and PT, relationship, intensity, time to onset, and duration
- All SAEs that occur throughout the study by SOC and PT, relationship and seriousness criteria
- All AESIs reported 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 concentrations
- GM of concentrations ratio (post- / pre-vaccination)

Immunogenicity – Stage II infants

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:

- Percentage of subjects with a PD3 and PD4 serotype specific IgG concentrations ≥ 0.35 µg/mL
- GM of serotype specific concentrations / titers (pre-dose 1[a], PD3, pre-dose 4, PD4)
- GM of serotype specific concentrations / titers ratio (PD3/pre-dose 1[a], PD4/pre-dose 4)

In addition, difference between any SP0202 formulations and Prevnar 13 groups, in term of percentages of subjects with serotype specific IgG concentration ≥ 0.35 µg/mL and 95%CI at PD3, as well of GM ratio between groups and 95%CI at PD3 and PD4, may be also presented.

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.

RCDCs of individual concentrations / titers will be presented for all serotypes. Further analyses may be described in the Statistical Analysis Plan (SAP).

[a] Not applicable from protocol Version 5.0

12.1.2 Hypotheses and Statistical Methods for Secondary Objective(s)

12.1.2.1 Hypotheses

12.1.2.2 Statistical Methods

12.1.2.2.1 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 subjects with a serotype specific titers above or equal to LLOQ

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 subjects with concentration / titer above predefined threshold, including those defining seroprotection
- Vaccine response for pertussis (PT, FHA, PRN, and FIM) antigens

12.1.2.2.2 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 subjects with a PD3 and PD4 serotype specific titers 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)

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[a] for RotaTeq and diphteria, tetanus, and Pertussis antigens, at PD3 for ENGERIX-B[b], RotaTeq, and Pentacel; at PD4 for M-M-RII and VARIVAX)
- Percentage of subjects with concentrations / titers above predefined thresholds, including those defining seroprotection (at PD3 and PD4 as applicable)

For all immunogenicity analyses, RCDCs of individual concentrations / titers will be presented for all serotypes / antigens.

Further analyses may be described in the SAP.

12.2 Analysis Sets

12.2.1 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 subjects to Groups 1 to 4 who received at least 1 dose of the study vaccine and had a valid post-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 subjects 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 subjects 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)

12.2.2 Safety Analysis Set

The safety analysis set (SafAS) is defined as those subjects who have received at least one dose of the study vaccines and have any safety data available. All subjects 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.

[a] Not applicable from protocol Version 5.0

[b] Immunogenicity to ENGERIX-B will be presented according to the number of doses received

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

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

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject 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
- Subject did not provide the post-dose serology sample V02 in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited medication or vaccine (identified among category 2 and 3, see Section 6.7)

In addition to the reasons listed above, subjects 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 subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS2 Infants Primary series:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject received a vaccine schedule other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window
- Subject did not provide the post-dose serology sample V04 in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited medication or vaccine (identified among category 2 and 3, see Section 6.7)

In addition to the reasons listed above, subjects 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 subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS3-Infants Booster dose:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject 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
- Subject 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)
- Subject did not provide the post-dose serology sample V06 in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited medication or vaccine (identified among category 2 and 3, see Section 6.7)

In addition to the reasons listed above, subjects 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).

The list can be completed at the time of SAP writing and before database lock.

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

12.2.4 Populations Used in Analyses

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

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

12.3 Handling of Missing Data and Outliers

12.3.1 Safety

No replacement will be done. Nevertheless, missing relationship will be considered as related at the time of stat analysis. Details will be described in the SAP.

12.3.2 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 < LLOQ will be converted to a value of 0.5 LLOQ.

For the calculation of 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) will be converted to ULOQ.

12.4 Interim / Preliminary Analysis

Early Safety data Review

[redacted]

The DMC review will be in an unblinded manner and the Sponsor SMT review will be blinded. The DMC reports will be provided by an independent statistician and won't be communicated to the Sponsor.

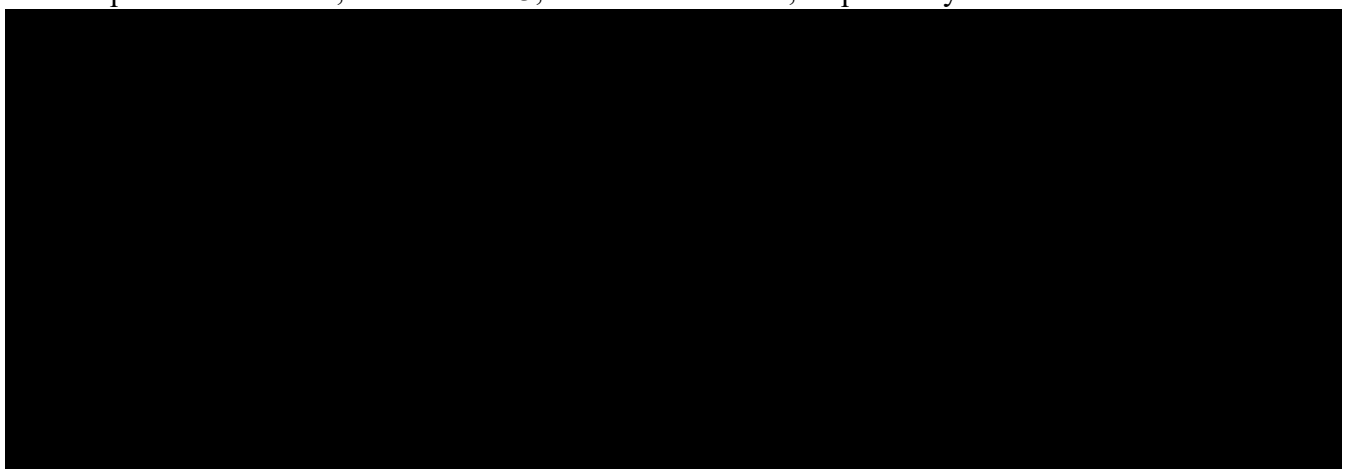
Statistical analysis

[redacted]

12.5 Determination of Sample Size and Power Calculation

The number of subjects 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 subjects per group (140 toddlers) in Stage I and 175 subjects 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 subjects per group is anticipated for toddlers, infants at PD3, and infants at PD4, respectively.



13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Study / Good Clinical Practice

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and / or national regulations and directives.

13.2 Source Data and Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets. The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

For missing or discrepant data on a diary card, the study coordinator will obtain verbal clarification from the subject, enter the response into the "Investigator's comment" page of the diary card, and transfer the information to the CRB.

The subject pre-screening log should list all individuals contacted by the Investigators to participate in the study, regardless of the outcome.

The Investigator must print[a] any electronic records on an ongoing basis, sign and date them immediately after creation, and keep the printouts on file as source documents that can be verified by the Sponsor or an inspector against the electronic records. Any subsequent changes of an electronic record require the record to be re-printed, dated (with an indication of the date of change), and signed. Such records must also be kept together with the original printed copy.

Good Documentation Practice should be followed by the Investigator and the site staff managing source documents.

13.3 Confidentiality of Data, Data Protection, and Access to Subject Records

Prior to initiation of the study, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur. In the event a subject's medical records are not at the investigational site, it is the responsibility of the Investigator, with the parent's / guardian's consent, to obtain those records if needed.

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations, including the GDPR (Global Data Protection Regulation). Data

[a] Unless the electronic medical records are managed by validated computerized systems that are compliant with US 21 CFR Part 11, in which case they are acceptable on their own.

collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Subjects' race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on a African-American population for the Food and Drug Administration [FDA]).

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

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

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

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

Before the start of the study (ie, before the inclusion of the first subject in the first center), the Investigators and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, visit timing, safety procedures, informed consent procedures, SAE reporting procedures, CRB completion, and the handling of samples and products. The Sponsor's staff or a representative will ensure and document that all material to be used during the study has been received at the site; and that the study Investigator team and local Sponsor/delegate staff have been properly informed about the study, GCP and regulatory requirements, and the Sponsor's procedures. Specific training sessions for the study Investigator team and the CRAs on these topics may be performed as necessary, and should be documented.

The following instruction manuals will be provided: the CRF Completion Instructions for entering data into the CRB, and the Operating Guidelines for detailed study procedures such as the product management and sample-handling procedures.

After the start of the study, the Sponsor's staff or a representative will be in regular contact with the investigational team through telephone calls and regular follow-up visits. The Investigator or delegate must be available for these visits, and must allow the Sponsor/delegate staff direct access to subject medical files and CRBs. During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the study progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)

- Source-verify completed CRBs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (eg,, protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed and the data have been entered into the CRB, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the study, a close-out visit will be performed to ensure that:

- The center has all the documents necessary for archiving
- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's Clinical Quality Assessment department (CQA) or by independent auditors to verify that the study has been conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. The Investigator must allow direct access to study documents during these inspections and audits.

13.4.3 Archiving

The Investigator and the study site shall retain and preserve 1 copy of the study file containing the essential documents related to the study and records generated during the study ("Study File") for the longer of the 2 following periods ("Retention Period"):

- 25 years after the signature of the final study report or
- Such longer period as required by applicable regulatory requirements

If during the Retention Period, the study site is no longer able to retain the Study File due to exceptional circumstances (such as bankruptcy), the study site shall contact the Sponsor to organize the transfer of the Study File to the Sponsor's designee at the Sponsor's expense. Following the Retention Period, the Investigator and/or the study site are responsible to dispose of the Study File according to the applicable regulations. Patient medical records shall be retained in compliance with local regulations.

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and all other documents related to the study will be kept by the Sponsor in the Trial Master File (TMF). Data on AEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

A Clinical Trial Agreement will be signed by all the parties involved in the study's performance, if relevant. The Sponsor has an insurance policy to cover any liabilities that may arise from use of the product and / or the study protocol.

13.6 Stipends for Participation

The subject may be provided with a stipend according to local practice to compensate for the time and travel required for study visits and procedures.

13.7 Publication Policy

Data derived from this study are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the study must be submitted to Sanofi Pasteur for review before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives recognition to the study group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

Sanofi Pasteur must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study at least 90 days prior to submission for publication / presentation. Any information identified by Sanofi Pasteur as confidential must be deleted prior to submission, it being understood that the results of this study are not to be considered confidential.

Sanofi Pasteur's review can be expedited to meet publication guidelines.

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