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Title Page

Protocol Title:

Safety and Immunogenicity of a Pneumococcal Conjugate Vaccine in Healthy Adults Aged 50 to 84 Years

Study Code: PSK00009

Protocol Version Number: 3.0

Amendment Number: 1

Compound: 21-valent pneumococcal conjugate vaccine, SP0202

Study Phase: II

Short Title:

Study of a Pneumococcal Conjugate Vaccine in Adults Aged 50 to 84 Years.

Sponsor Name and Legal Registered Address:

Sanofi Pasteur Inc.
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Manufacturer:

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Regulatory Agency Identifier Number(s):

BB-IND: 018207

Approval Date: 30 November 2020

Medical Monitor Name and Contact Information are provided in the Operating Guidelines.

The study centers, the Investigators at each center, and the Coordinating Investigators are listed in a separate document.

Document History

Previous Version	Date	Comments
1.0	26 May 2020	Version submitted and approved by IRB / IEC. Updated in response to comments provided by the Health Authorities (CBER) prior to study initiation.
2.0	**24 August 2020**	**First version used in the study at the time of FVFS**

IRB: Institutional Review Board; IEC: Independent Ethics Committee

Overall Rationale for the Amendment:

The study has been amended to add a Data Monitoring Committee (DMC) review. An unblinded review will be performed by the DMC when at least 150 participants have been vaccinated and have safety data up to 30 days after injection available. The results from this DMC review will be supportive to the Sponsor decision-making process as regards to the SP0202 clinical development plan.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

Safety and Immunogenicity of a Pneumococcal Conjugate Vaccine in Healthy Adults Aged 50 to 84 Years

Short Title:

Study of a Pneumococcal Conjugate Vaccine in Adults Aged 50 to 84 Years

Rationale:

The SP0202 investigational vaccine is intended to provide protection against diseases caused by the *Streptococcus pneumoniae* serotypes included in the vaccine, in population from infants to elderly. There are two types of pneumococcal vaccines available in the United States: Prevnar 13 (a 13-valent conjugated vaccine) and Pneumovax 23 (a 23-valent unconjugated vaccine). Both vaccines are recommended in the US population aged 65 years or above (1). SP0202 investigational vaccine contains 21 serotypes that are conjugated to carrier protein. PSK00009 is a Phase II study that will evaluate the immunogenicity and safety of 3 SP0202 formulations that differ by the antigen content for a few serotypes, administered as a single dose to healthy adults aged 50 to 84 years. Two groups will serve as control and receive a single dose of either Prevnar 13 or Pneumovax 23.

Objectives and Endpoints:

Objectives	Endpoints
Immunogenicity To assess the immune response of the 3 SP0202 formulations, Prevnar 13, and Pneumovax 23 30 days after the administration of the single dose vaccination	• Serotype specific OPA titers for all pneumococcal serotypes included in the SP0202 formulations, as determined by multiplex opsonophagocytic assay (MOPA), at baseline (D01) and 30 days after vaccination (D31) • Serotype specific OPA titers ratio (post/pre-injection) for all pneumococcal serotypes included in the SP0202 formulations as determined by MOPA • Serotype-specific IgG concentrations for all pneumococcal serotypes included in the SP0202 formulations as measured by electro-chemiluminescence assay (ECL), at baseline (D01) and 30 days after vaccination (D31) • Serotype-specific IgG concentration ratios (post/pre-vaccination) for all pneumococcal serotypes included in the SP0202 formulations as measured by ECL

Safety To assess the safety profile of the 3 SP0202 formulations, Prevnar 13, and Pneumovax 23	• Presence of any unsolicited systemic AEs reported in the 30 minutes after injection of a SP0202 formulation, Prevnar 13, or Pneumovax 23 • Presence of solicited (ie, pre-listed in the participant's DC and in the case report form (CRF)) injection site reactions occurring up to 7 days after the day of injection (D08) of a SP0202 formulation, Prevnar 13, or Pneumovax 23 • Presence of solicited (ie, pre-listed in the participant's DC and in the CRF) systemic reactions occurring up to 7 days after the day of injection (D08) of a SP0202 formulation, Prevnar 13, or Pneumovax 23 • Presence of unsolicited (spontaneously reported) AEs up to 30 days after the day of injection (D31) of a SP0202 formulation, Prevnar 13, or Pneumovax 23 • Presence of SAEs and AESIs, throughout the study period (up to 6-month follow-up)

Overall Design

Type of design	Parallel, multicenter (approximately 8 sites)
Phase	II
Control method	Active -controlled (controls = Prevnar 13 and Pneumovax 23)
Study population	Healthy adults aged 50 to 84 years
Countries	United States of America
Level and method of blinding	Modified double-blind (observer-blind)
Study intervention assignment method	Randomization with stratification by sites and age group (ie 50-64 years and 65 to 84 years)
Review group	Safety Management Team (SMT) and Data Monitoring Committee

Disclosure Statement:

This is a parallel group prevention study with 5 groups that is Participant, Investigator and Outcomes Assessor blinded.

Number of Participants:

A total of 750 participants, approximatively 150 in each group (approximately 375 participants aged 50 to 64 years and 375 participants aged 65 to 84 years) are expected to be randomized.

Group	Number of Participants	Formulation Name
Group 1	150	SP0202-IIb
Group 2	150	SP0202-VI
Group 3	150	SP0202-VII
Group 4	150	Prevnar 13®
Group 5	150	Pneumovax 23®

Intervention Groups and Duration:

Eligible participants will be randomized in a 1:1:1:1:1 ratio to receive a single intramuscular (IM) injection of either 1 of the 3 SP0202 formulations or Prevnar 13 or Pneumovax 23 at Day (D)01.

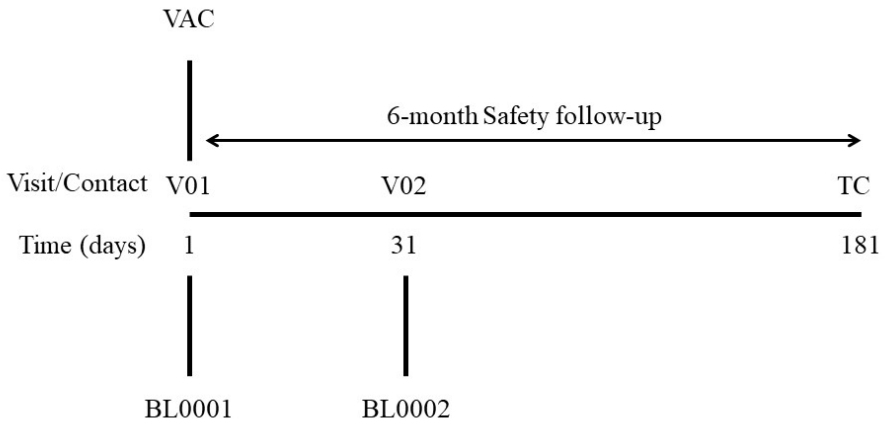
The duration of each participant's participation will be approximately 6 months.

***Data Monitoring Committee*:** Yes

1.2 Schema

The graphical design of PSK00009 study is presented in Figure 1.1.

Figure 1.1: Graphical study design



BL: Blood sample
VAC: vaccination
TC: telephone call

1.3 Schedule of Activities (SoA)

Visits procedures are detailed in the Operating Guidelines.

Table 1.1: Schedule of activities

Phase II Study, 2 Visits, 1 Phone Call, 1 Vaccination, 2 Blood Samples, Approximately 6 Months Duration Per Participant

Visit/Contact	*Collection of information in the CRF*	Visit 1	Visit 2*	Phone call 6-month safety follow-up
Study timelines (days)		D01	D31	D181
Time windows (days)		NA	[+14 D]	+14
Visit procedures:				
Informed consent	X	X		
Inclusion/exclusion criteria	X	X		
Collection of demographic data†	X	X		
Urine pregnancy test (if applicable)‡		X		
Collection of Medical history	X Significant Medical History	X		
Physical examination (including body temperature)§		X	X	
Randomization/allocation of participant number	X	X		
Blood sampling (BL), 20 mL	X	BL0001 Pre-vac	BL0002	
Vaccination (vac)	X	X		
Immediate surveillance (30 min)	X	X		
Diary card provided**		X		
Collection of solicited injection site and systemic reactions	X	D01 – D08		
Collection of unsolicited adverse events (AEs)	X	To be reported at any time from D01 to D31		
Diary card reviewed and collected			X††	
Memory aid provided			X	
Telephone call				X
Memory aid reviewed				X‡‡

Collection of concomitant medications	X Reportable concomitant medication	X	X	
Collection of serious and non-serious adverse events of special interest (AESIs)	X	To be reported at any time during the study		
Collection of serious adverse events (SAEs)	X	To be reported at any time during the study		
Collection of pregnancies	X	To be reported at any time during the study		
End of Active Phase participation record	X		X	

* The investigator or an authorized designee will interview the participant to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

† To comply with US FDA expectations, Sponsors are to enroll participants who reflect the demographics for clinically relevant populations with regard to age, gender, race and ethnicity as described in https://www.fda.gov/downloads/regulatoryinformations/guidances/ucml126396.pdf.

‡ In female participants of childbearing potential (ie, not post-menopausal for at least 1 year, or surgically sterile).

§ Physical examination based on medical history will be performed at Visit 1. Targeted physical examination may also be performed at Visit 2, as necessary.

** Participants will use this diary card to record information about solicited reactions from D01 to D08, as well as unsolicited AEs, SAEs, and AESIs until Visit 2.

†† Staff will collect the diary card at Visit 2, and review any solicited reactions ongoing at Visit 2, Unsolicited AEs, concomitant medication, SAEs and AESIs.

‡‡ During this call the staff will review the memory aid with the participant and determine whether the participant experienced any SAE or AESI not yet reported.

CRF: case report form

2 Introduction

2.1 Study Rationale

The SP0202 investigational vaccine is intended to provide protection against disease caused by the *Streptococcus pneumoniae* serotypes included in the vaccine, in population, from infants to elderly. Compared to the licensed vaccines Prevnar 13 and Pneumovax 23, SP0202 investigational vaccine contains 21 serotypes:13 serotypes common to those of Prevnar 13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) and 8 additional serotypes (8, 9N, 10, 11A, 12F, 15B, 22F, 33F); the later are common to Pneumovax 23. These 21 serotypes are conjugated to 2 different protein carriers, either tetanus toxoid (TTxd) or cross-reacting material 197, a non-toxic mutant of diphtheria toxin (CRM_{197}). These two protein carriers included in the PCV21 formulation have proven safety records. The long-term benefit of unconjugated vaccines in elderly population was recently discussed as their protection-induced is weak and short lived because of the absence of B-cell memory production following immunization (2) (3). Therefore, the conjugation technology using a carrier protein to polysaccharides has been used to increase immunogenicity in elderly population. 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.

Four formulations of SP0202 investigational vaccine (with different content of serotypes and different serotypes conjugated to either TTxd or CRM_{197}) were evaluated in Phase I study PSK000007. They differed by the number of serotypes conjugated to TTxd (2 or 4) and by the dosage of some serotype specific polysaccharides compared to existing PCV13. (Table 2.2).

Table 2.1: Specificities of the 4 formulations evaluated in Phase I study PSK00007

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

Based on PSK00007 safety and immunogenicity results, 3 formulations designed to optimize SP0202 immunogenicity and secure the identification of a lead formulation for Phase III have been developed (see Table 6.1 for their composition). All 3 formulations will include 4 serotypes conjugated to TTxd (serotypes 1, 5, 15B and 22F). It is to be noted that the TTxd content will be decreased compared to SP0202-II formulation tested in the Phase I study following changes in the manufacturing process of serotypes 15B and 22F (increased polysaccharide / tetanus toxoid ratio, expected to improve immune response).

With regards to the antigen content per serotypes:

- Formulation IIb will include [redacted] µg for all serotypes but 6B ([redacted] µg)
- Formulation VI will differentiate from IIb with serotypes 3, 19A and 19F at [redacted] µg
- Formulation VII will differentiate from IIb with serotypes 3, 4, 9V, 19A and 19F at [redacted] µg

The SP0202 investigational vaccine is designed for immunization of infants/toddlers and elderly against pneumococcal disease. Phase II study PSK00008 including toddlers aged 12-15 months, and infants aged 42 to 89 days will be conducted in parallel with the current Phase II study PSK00009 including healthy adults aged 50 to 84 years.

2.2 Background

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 (4) (5) (6). The most common disease-causing serotypes observed throughout the world are generally similar. However, there may be large variations in the relative serotype prevalence in these regions, particularly between developed and developing countries (7).

The microorganism, through the asymptomatic colonization of the nasopharynx, is a major cause of several infections, including pneumonia, meningitis, bacteremia, sinus and otitis media (6). Infections characterized by the isolation of *S. pneumoniae* from a normal sterile site, such as blood, cerebrospinal fluid, or synovial fluid, identified as occurrences of invasive pneumococcal disease (IPD).

In order to offer protection against *S. pneumoniae* infections, vaccines against serotype specific capsular polysaccharides have been developed. The first pneumococcal polysaccharide vaccines (PPSV) were brought to the market in 1947 and offered protection against serious infections caused by 6 serotypes of *S. pneumoniae*. In 1977, the first 14-valent vaccine was licensed and in 1983 the vaccine coverage was expanded to 23 *S. pneumoniae* serotypes (8). In the following years, 23-valent PPSVs were shown to reduce the risk of IPD in adults (9), although protection against pneumococcal pneumonia has not yet been convincingly demonstrated (10) (11). In addition, PPSVs have shown a poor immunogenicity in children aged less than 2 years (ie, the most vulnerable age group to pneumococcal infections), an inability to generate immune memory at any age, and no effect on pneumococcal carriage (12) (13) (14).

As a way to offer a stronger and longer-lasting protection to populations in which PPSVs are the least immunogenic (ie, children under 2 years, adults over 65 years, and immunocompromised persons), second generation pneumococcal vaccines have been developed by conjugating *S. pneumoniae* capsular polysaccharides with carrier proteins to induce both humoral and cellular immune response (12). Pneumococcal conjugate vaccines (PCVs) have been shown to be effective in preventing pneumococcal pneumonia, IPD, and otitis in children (15) (16) (17) (18) (19) (20).

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 (13) (14). 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 (13) (21) (22). PCVs have had an important impact on public health in developed countries, as well as worldwide; since global roll out (9).

However, it is now acknowledged that serotypes covered by marketed PCVs tend to be replaced as pathogens by other circulating serotypes (21) (23) (24). Less fit or emergent serotypes simply take advantage of an ecological niche left vacant (25). One of most notable examples is serotype 19A which emerged as a predominant serotype in several countries with no PCV7 vaccination programs (7).

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 complementary antigens, one to prevent colonization (ie, pneumococcal polysaccharides) and another to limit virulence transition (ie, protein antigens that selectively target pneumococci virulence transition) (26). The proof of concept of such an approach has not been demonstrated to date. 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 forwards with the latter approach, a next generation of 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.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events, the potential risks, and uncertainties of SP0202 may be found in the Investigator's Brochure (IB).

[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) absorbed, GlaxoSmithKline Biological S.A.

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

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.2

Table 2.2: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: SP0202		
• Anaphylaxis • Guillain-Barré Syndrome • Arthus-type hypersensitivity • Gastrointestinal disorders (vomiting) • Headache • Myalgia, arthralgia Refer to IB Section 6 for more information regarding potential risks	All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine. Refer to the IB Section 5 and Section 6 for more information regarding the data from previous experience with the investigated vaccine.	Exclusion criteria 8 and 9 for those at increased risk. Observation period after vaccination for early detection and treatment.
Comparator: Prevnar 13		
Refer to the package insert for more information regarding potential risks.	Identified and potential risks observed in clinical trials and/or post-marketing surveillance.	Exclusion/inclusion criteria take in account contraindications, warnings and precautions as defined in product label.
Comparator: Pneumovax 23		
Refer to the package insert for more information regarding potential risks.	Identified and potential risks observed in clinical trials and/or post-marketing surveillance.	Exclusion/inclusion criteria take in account contraindications, warnings and precautions as defined in product label.
Study Procedures		
Vasovagal reactions (syncope), or psychogenic reactions to needle (vaccine injection or blood sampling).	Anxiety-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection or blood draw, and may be accompanied by several neurological signs such as transient visual disturbance, paresthesia or seizure-like activity.	Observation period after vaccination for early detection and treatment.

2.3.2 Benefits from Study Participation

Four 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] Based on PSK00007 results, 3 formulations have been selected for further evaluation in the target population. These 3 formulations will be evaluated in this Phase II study. It is expected that adults aged 50 to 84 years who will be vaccinated with SP0202 will develop an immune response against the 21 serotypes, although there is no guarantee.

Participants 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).

Participants who will receive Pneumovax 23 will likely be protected against pneumococcal disease due to 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F).

As with any vaccines, SP0202 formulations and Prevnar 13, and Pneumovax 23, vaccines administered during the study may not protect 100% of individuals against the disease they are designed to prevent.

2.3.3 COVID-19 risk assessment

SP0202 is a pneumococcal vaccine. It would not cause immune suppression. Therefore, the risk that a participant in this study will contract Covid-19 disease solely due to the administration of the study vaccine will be similar to the risk that a person not participating in this study will contract Covid-19. However, the risk of exposure to infected people cannot be completely excluded as the participants may need to expose to public area (eg, commute to the site and at the site).

2.3.4 Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to participants enrolled in this study, the potential risks that may result from study participation are balanced by the anticipated benefits that may be afforded to participants.

3 Objectives and Endpoints

Table 3.1: Objectives and endpoints

Objectives	Endpoints
Immunogenicity To assess the immune response of the 3 SP0202 formulations, Prevnar 13, and Pneumovax 23, 30 days after the administration of the single dose vaccination	• Serotype-specific OPA titers for all pneumococcal serotypes included in the SP0202 formulations, as determined by multiplex opsonophagocytic assay (MOPA), at baseline (D01) and 30 days after vaccination (D31) • Serotype-specific OPA titers ratio (post/pre-injection) for all pneumococcal serotypes included in the SP0202 formulations as determined by MOPA • Serotype-specific IgG concentrations for all pneumococcal serotypes included in the SP0202 formulations as measured by electro-chemiluminescence assay (ECL), at baseline (D01) and 30 days after vaccination (D31) • Serotype-specific IgG concentration ratios (post/pre-injection) for all pneumococcal serotypes included in the SP0202 formulations as measured by ECL
Safety To assess the safety profile of the 3 SP0202 formulations, Prevnar 13, and Pneumovax 23	• Presence of any unsolicited systemic AEs reported in the 30 minutes after injection of a SP0202 formulation, Prevnar 13, or Pneumovax 23 • Presence of solicited (ie, pre-listed in the participant's DC and in the CRF) injection site reactions occurring up to 7 days after the day of injection (D08) of a SP0202 formulation, Prevnar 13, or Pneumovax 23 • Presence of solicited (ie, pre-listed in the participant's DC and in the CRF) systemic reactions occurring up to 7 days after the day of injection (D08) of a SP0202 formulation, Prevnar 13, or Pneumovax 23 • Presence of unsolicited (spontaneously reported) AEs up to 30 days after the day of injection (D31) of a SP0202 formulation, Prevnar 13, or Pneumovax 23 • Presence of SAEs and AESIs, throughout the study period (up to 6-month follow-up)

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Parallel, multicenter
Phase	II
Control method	Active-controlled (controls = Prevnar 13 and Pneumovax 23)
Study population	Healthy adults aged 50 to 84 years
Level and method of blinding	Modified double-blind (observer-blind)
Study intervention assignment method	Randomization with stratification by sites and by age group
Number of participants	750 participants, approximately 150 in each group (approximately 375 aged 50 to 64 years and 375 aged 65 to 84 years)
Intervention groups	In each site and age group, randomization in a 1:1:1:1:1 ratio to receive a single injection of either 1 of the 3 formulations of SP0202, Prevnar 13, or Pneumovax 23
Total duration of study participation	Approximately 6 months
Countries	United States of America
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	Yes

4.2 Scientific Rationale for Study Design

PSK00009 is a Phase II study that will evaluate the immunogenicity and safety of 3 SP0202 formulations administered as a single dose to healthy adults aged 50 to 84 years naïve to prior pneumococcal vaccine administration. Two groups will serve as controls and receive a single dose of either Prevnar 13 or Pneumovax 23.

In the US, pneumococcal vaccination with Prevnar 13 (a 13-valent conjugated vaccine) or Pneumovax 23 (a 23-valent unconjugated vaccine) is recommended by ACIP as follows (27):

- Pneumovax 23: for all immunocompetent adults ≥ 65 years old (yo), for people 19 to 64 yo with certain conditions and for adults 19 to 64 yo who smoke cigarettes.
- Prevnar 13: in adults with certain medical conditions, for immunocompetent adults ≥ 65 yo who have not previously received Prevnar 13 based on shared clinical decision-making.

In this study, Prevnar 13 will serve as a reference vaccine for safety assessment and for immunogenicity of the 13 common serotypes with SP0202. Pneumovax 23 will provide a reference for the immune response to the 8 additional serotypes in SP0202 formulations.

Given the acceptable safety data generated in PSK00007 study (Phase I study), no early safety data review is planned for this study. The safety will be continuously monitored by the Sponsor. The safety data collected will be entered into the CRF and summarized by the Sponsor. Blinded reviews will be performed by the Sponsor during the Safety Management Team (SMT) meetings. An unblinded review by a Data Monitoring Committee (DMC) will also be conducted to assess the safety data, including AESIs, SAEs and safety profile of each SP0202 formulation when at least 150 participants have been vaccinated and have safety data up to D31 (30 days after injection) available. The DMC will also review the unblinded safety data collected on all participants up to D31.

Due to differences in the appearance of SP0202, Prevnar 13, and Pneumovax 23 products, the study will have an observer-blinded design (double-blind across SP0202 formulations) to limit any bias in the assessment of safety. The designated vaccine preparer(s)/administrator(s) will be unblinded given the different aspect of the products, but neither the participant nor the investigator nor the study staff in charge of vaccination will know which vaccine will be administered. The unblinded designated vaccine preparer(s)/administrator(s) will not be involved in any of the blinded study assessments (eg, immunogenicity, safety). The Investigators (or delegate) in charge of safety assessment, the study staff who collect the safety data, and the laboratory personnel who analyze the blood samples will not know which product was administered.

Note: at this stage and based on currently available information, this is not known whether prior history of exposure to SARS-CoV-2 (2019-nCoV) would impact the immune response to pneumococcal vaccines. 2019-nCoV serology screening prior to vaccination is not included. However, serum samples could be tested to determine participants' sero-status regarding 2019-nCOV at the time of the study if deemed necessary according to the available scientific knowledge. This assessment may be done during immunogenicity assessment or at any time.

4.3 Justification for Dose

The vaccination schedule of a single dose for pneumococcal vaccine in elderly population is per standard procedure recommended by CDC (1).

The antigen content for each serotypes is similar to Prevnar 13, except for serotypes 3, 19A and 19F in formulation SP0202 VI and serotypes 3, 4, 9V, 19A, and 19F in formulation VII.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed the last phone call planned in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the clinical study report is finalized.

5 Study Population

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

5.1 Inclusion Criteria

Participants are eligible for the study only if all of the following criteria are met:

I01: Aged 50 to 84 years on the day of inclusion[a].

I02: Informed consent has been signed and dated.

I03: Able to attend all scheduled visits and to comply with all trial procedures.

5.2 Exclusion Criteria

Participants are not eligible for the study if any of the following criteria are met:

E01: Participant is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, or surgically sterile.

E02: Participation at the time of the study enrollment (or in the 4 weeks preceding the trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device or medical procedure

E03: Receipt of any vaccine in the 4 weeks preceding the trial vaccination or planned receipt of any vaccine from enrollment through the last blood sampling Visit, except for influenza vaccination, which may be received at least 2 weeks before study vaccine. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

E04: Previous vaccination against *S. pneumoniae* with either a pneumococcal conjugated vaccine (PCV) or a pneumococcal polysaccharide vaccine (PPSV).

E05: Receipt of immune globulins, blood or blood-derived products in the past 3 months.

E06: 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).

[a] "50 to 84 years" means from the day of the 50th birthday to the day before the 85th birthday

E07: History of *S. pneumoniae* infection or disease, confirmed either serologically, or microbiologically.

E08: History of Guillain-Barré syndrome occurring within 6 weeks after a prior dose of a TTxd-containing vaccine.

E09: Experienced an Arthus-type hypersensitivity reaction following a prior dose of a TTxd-containing vaccine < 10 years ago.

E10: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances[a].

E11: Verbal report of thrombocytopenia contraindicating IM vaccination in the Investigator's opinion

E12: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination in the Investigator's opinion.

E13: At risk of invasive pneumococcal disease (eg, participant with functional or anatomic asplenia, participants with severe asthma, participants travelling to countries with high endemicity).

E14: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.

E15: Current alcohol abuse or drug addiction.

E16: Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion[b].

E17: Any condition that in the opinion of the Investigator could interfere with the evaluation of the vaccine (eg, under investigation or monitoring for possible coronavirus disease 2019 [COVID-19])

E18: Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F). A prospective participant should not be included in the study until the condition has resolved or until 3 days after the febrile event has subsided.

E19: Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw.

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[a] The component of the SP0202 formulations are listed in Section 6.1 and in the Investigator's Brochure. The components of Prevnar 13 and Pneumovax 23 are listed in Section 6.1 and in their prescribing information.

[b] Participants with pre-existing stable chronic condition, determined based on medical history and clinical judgement of the investigator are eligible.

E20: Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study.

If the participant has a primary physician who is not the Investigator, the site should contact this physician with the participant's consent to inform him / her of the participant'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.

5.3 Lifestyle Considerations

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

5.4 Screen Failures

Screen failures are defined as participants who are contacted by the sites and agree to participate in the clinical study but are not subsequently randomly assigned to study intervention because they do not meet the criteria for participation in the study (eg, inclusion and/or exclusion criteria). Screening information is recorded in the source documents.

Individuals who do not meet the criteria for participation in this study (screen failure) cannot be rescreened.

6 Study Intervention

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

Note: routine vaccine administered outside of study protocol are not considered as study interventions.

6.1 Study Intervention(s) Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study intervention(s)

Group Name	Group 1 SP0202-IIb	Group 2 SP0202-VI	Group 3 SP0202-VII	Group 4 Prevnar 13	Group 5 Pneumovax 23
Intervention Name	Pneumococcal Conjugate Vaccine	Pneumococcal Conjugate Vaccine	Pneumococcal Conjugate Vaccine	Pneumococcal 13-valent Conjugate Vaccine	Pneumococcal Vaccine Polyvalent
Use	Experimental	Experimental	Experimental	Active comparator	Active comparator
IMP and NIMP	IMP	IMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine
Dose Formulation	Suspension for injection in a pre-filled syringe	Suspension for injection in a pre-filled syringe	Suspension for injection in a pre-filled syringe	Suspension for injection in a pre-filled syringe	Solution for injection in a pre-filled syringe
Unit Dose Strength(s)	[redacted] µg of polysaccharide from *S. pneumoniae* serotypes 3, 4, 6A, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 18C, 19A, 19F, 23F, 33F, and [redacted] µg of polysaccharide for serotype 6B; individually conjugated to CRM_{197} protein [redacted] µg of polysaccharide from pneumococcal serotypes 1, 5, 15B and 22F individually conjugated to TTxd carrier protein	[redacted] µg of polysaccharide from *S. pneumoniae* serotypes 4, 6A, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 18C, 23F, 33F, and [redacted] µg of polysaccharide for serotypes 3, 6B, 19A, and 19F; individually conjugated to CRM_{197} protein [redacted] µg of polysaccharide from pneumococcal serotypes 1, 5, 15B, and 22F individually conjugated to TTxd carrier protein	[redacted] µg of polysaccharide from *S. pneumoniae* serotypes 6A, 7F, 8, 9N, 10A, 11A, 12F, 14, 18C, 23F, 33F, and [redacted] µg of polysaccharide for serotypes 3, 4, 6B, 9V, 19A, and 19F; individually conjugated to CRM_{197} protein [redacted] µg of polysaccharide from pneumococcal serotypes 1, 5, 15B, and 22F; individually conjugated to TTxd Carrier protein	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 CRM_{197} protein	25 µg of polysaccharide from *S. pneumoniae* serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F

Excipients / Diluent	[redacted]			Succinic acid, NaCl, Polysorbate 80 , aluminum (0.125 mg) and water for injection	NaCl, Phenol and water for injection
Dosage Level	0.5 mL per dose				
Number of doses / Dosing Interval	1 dose				
Route of Administration	IM injection				
Site of Administration	Deltoid muscle in the upper arm				
Injection Site Side	On the arm opposite to blood sample				
Sourcing	Provided by the Sponsor				
Packaging and Labeling	Each study intervention will be provided in an individual box. All will be labeled as required per country requirement.				
Current/Former Name(s) or Alias(es)	Not applicable	Not applicable	Not applicable	Prevnar 13®	Pneumovax®23
Batch Number	TBD	TBD	TBD	TBD	TBD

IMP: Investigational Medicinal Product; NIMP: Non-Investigational Medicinal Product; CRM_{197}: Cross-Reacting material 197; TBD: To be determined

6.2 Preparation/Handling/Storage/Accountability

Detailed guidance and information are provided in the Operating Guidelines.

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the Operating Guidelines.

5) Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content, and extraneous particulate matter and / or discoloration, whenever solution or container permit. If one 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.
6) Since some study intervention are a suspension containing an adjuvant, it has to be shaken vigorously prior use to obtain a homogenous suspension. Do not use the study intervention if it cannot be resuspended.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

This study will be a randomized, modified double-blind study for 5 vaccine groups.

On the day of enrollment, participant who meet the inclusion/exclusion criteria and sign the informed consent form (ICF) will be randomly assigned to Groups 1 through 5 in a 1:1:1:1:1 ratio, stratified according to sites and age group such that each group will have approximately 150 participants (around 75 participants aged 50 to 64 years and around 75 participants aged 65 to 84 years).

The unblinded vaccinator or delegate 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 then provide the group assignment and have the site staff confirm it. The full detailed procedures for group allocation are described in the Operating Guidelines. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

Participant 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 participant identifier). The first digit of the participant identifier will be “1” for participants aged 50 to 64 years and “2” for participants aged 65 to 84 years. For example, Participant 840000210005 is the fifth participant aged 50 to 64 years enrolled in Center Number 2 in the US (840 being the US code country).

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT and an internal system.

6.3.2 Blinding and Code-breaking Procedures

The study will be performed in a modified double-blind fashion:

- The unblinded qualified trial staff member, independent of the immunogenicity and safety evaluations and other trial evaluations will administer the study intervention.
- The Investigators (or delegates) in charge of safety assessment, the trial staff who collect the safety data, and the laboratory personnel who analyze the blood samples will be blinded and not know which product was administered.
- The participant will not know which product was 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

The Investigator responsible for safety assessment will not attend the vaccination session but will be available in case of emergency (anaphylactic shock).

Treatment numbers will be used to identify each vaccine syringe for the purpose of randomization, vaccination and the recording of the study intervention administered. Treatment numbers will be randomly assigned to study interventions syringes. The IRT vendor will be responsible for assigning the treatment group identification and treatment number to be received by the enrolled participant. The participant, the Investigator, and the study staff members who collect the safety data and laboratory personnel who analyze the blood samples will all be blinded to the group assignment. The individual responsible for preparing / administering study intervention will not be authorized to collect any safety / serology data.

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 participant. Code-breaking should be limited to the participant(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 Responsible Medical Officer (RMO) if a participant'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 case report form (CRF) is to be completed.

The Independent Ethics Committees (IEC) / Institutional Review Boards (IRB) must be notified of the code-breaking, in accordance with local regulations. 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.

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

- by the Global Pharmacovigilance (GPV) Department through an internal system for reporting to Health Authorities in the case of an unexpected SAE considered causally related as described in International Council for Harmonization (ICH) E2A. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (ie, the participant'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.

A first statistical analysis of the safety and immunogenicity data obtained up to 30 days after vaccination (V02) will be conducted once data are available and an interim database lock has been conducted. The blind of participants will be broken for the analysis, but the randomization list will not be provided to Investigators until completion of the 6-month safety follow-up and will be kept internally. A final analysis will be conducted once the 6-month safety data has been collected and the final database lock has occurred. If the V01-V02 immunogenicity data release is planned at

the time or after the 6-month follow-up data availability, only one final database lock and one analysis including all data may be conducted.

The DMC will conduct an unblinded review of the safety data when at least 150 participants have been vaccinated and have safety data up to D31 (30 days after injection) available. The DMC will also conduct another unblinded review of the safety data collected on all participants up to D31. An unblinded external independent statistician will share the unblinded safety data with the DMC members. The information will not be communicated to either the Investigator or the Sponsor study team before the end of the trial and database lock.

If during the internal SMT/DMC 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.

The code-breaking procedures are described in the Operating Guidelines and in the DMC charter.

6.4 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 6.1), and that any noncompliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified and trained study personnel
- The person in charge of study intervention management at the site will maintain accountability records of study intervention delivery to the study site, study intervention inventory at the site, dose given to each participant, and unused or wasted doses

6.5 Concomitant Therapy

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

Documentation in the CRF 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 CRF from the day of vaccination (D01) to the end of the solicited and unsolicited follow-up period (D31 + 14 days).

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:

[a] Participant will be required to document in the DC all medications received.

- **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], systemic steroids/corticosteroids [therapy duration for less than 2 consecutive weeks])
- **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 IM vaccination], blood products, antibiotic classes taken within 3 day [72 hours] prior to blood draw that may interfere with bioassays used by the Global Clinical Immunology [GCI] department or other testing laboratories, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors, immune globulins in the 3 months preceding vaccination)
- **Category 3:** medications impacting or that may have an impact on both the safety and the immune response (eg, long-term systemic corticosteroids therapy [prednisone or equivalent for more than 2 consecutive weeks])

The information reported in the CRF 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[a] 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 steroids (inhaled, otic, ophthalmic, nasal etc.) 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 pre-listed categories. Medications will not be coded.

6.5.1 Rescue Medicine

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.

6.6 Dose Modification

Not applicable.

[a] Medication(s) prescribed for preventing AE occurrence (eg, paracetamol to reduce the risk of fever).

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Temporary contraindications

The following is a temporary contraindication to blood draw BL0002 at Visit 2:

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

Note: If a participant receives oral or injectable antibiotic therapy within 3 days prior to the blood draw, the Investigator will postpone that blood draw until it has been 3 days since the participant 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 this timeframe, the blood sample should be collected without postponement, and it should be documented appropriately (in source document and CRF) that the sample was taken less than 3 days after stopping antibiotic treatment.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF: Adverse Event, Lost to Follow-up, Protocol Deviation, or Withdrawal by participant.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

Follow-up of Discontinuations

For participants who have prematurely terminated the study, the site should attempt to contact them and complete all scheduled safety follow-ups, except if they specified that they do not want to be contacted again and it is documented in the source document.

For participants where the reason for early termination is lost to follow-up, the site will not attempt to obtain further safety information. See Section 7.3 for definition of “lost to follow-up”.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit or cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods), or at least to determine his/her health status while fully respecting his/her rights. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Blood samples will be collected as described in the SoA table (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 40 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Guidance and information for the sample collection, preparation, storage, and shipment are provided in the Operating Guidelines.

8.1 Efficacy and Immunogenicity Assessments

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

Multiplexed opsonophagocytic killing assay (MOPA)

This method will be performed on BL0001 and BL0002 collected on D01 and D31 respectively. Assays will be performed by PPD (a CRO laboratory), Richmond (VA), USA.

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

This method will be performed on BL0001 and BL0002 collected on D01 and D31 respectively.

Assays will be performed by Sanofi Pasteur Global Clinical Immunology (GCI), Swiftwater (PA), USA.

8.2 Safety Assessments

This section presents safety assessments other than adverse events which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Medical History

Prior to enrollment, participants 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 participant 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 CRF.

8.2.2 Physical Examinations

At Visit 1, the Investigator or a delegate will perform a physical examination based on medical history and including evaluation of the following body systems: general appearance, skin, head, eyes, ears, nose, throat, heart, lungs abdomen, musculoskeletal, extremities, neurological and lymph nodes examination. A targeted physical examination may also be performed at Visit 2, as necessary. Information will be recorded in the source document.

Temperature measurement will be done during the physical examination before vaccination and recorded in the source document.

8.2.3 Vital Signs

Axillary pre-vaccination temperature will be systematically collected by the investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used.

8.2.4 Clinical Safety Laboratory Assessments

Urine pregnancy testing will be performed in women of childbearing potential before vaccination.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.3.

AEs will be reported by the participants to the investigator, then by the investigator to the Sponsor.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

Participants will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination observation should be documented in the source document and immediate events will be recorded at D01 in the eCRF.

Reactogenicity

Solicited injection site reactions will be collected from D01 to D08 after vaccination.

Solicited systemic reactions will be collected from D01 to D08 after vaccination.

The solicited injection site reactions and systemic reactions that are pre-listed in the diary cards and CRF, together with the intensity scales, are presented in Appendix 10.3.5.1.1.

Unsolicited Non-serious Adverse Events

Unsolicited non-serious adverse events will be collected from D01 to D31 after vaccination.

The intensity grading scale for unsolicited non-serious adverse events is presented in Appendix 10.3.5.1.2.

Adverse Events of Special Interest (AESIs)

AESIs will be collected throughout the study period, from D01 until 6 months after vaccination.

See Section 8.3.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from D01 until 6 months after vaccination.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will not be recorded on the AE section of the CRF.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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

8.3.2 Method of Detecting AEs and SAEs

Individual diary cards, 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. These diary cards will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants 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 participants on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the participants to collect the information recorded in the diary card, 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 CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

The 6-month follow-up will be done by interviewing participants over the telephone using a questionnaire to capture SAEs and AESIs, if applicable.

The method of recording, evaluating, and assessing causal relationship of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

Unless a participant refuses further contact, each participant 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 participant's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the study intervention administered
- The AE caused the discontinuation of the participant from the study or from vaccination

The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those investigating medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Pregnancy is an exclusion criterion for enrollment in this study, but a participant could potentially become pregnant during her participation.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until delivery by the investigator and recorded in the Pregnancy CRF. Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.
- If a pregnancy is reported, the investigator should inform the Sponsor within 1 month of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 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. AESI will be collected throughout the study. AESI include the following:

- Anaphylaxis defined as per the Brighton collaboration case definition (28).

8.4 Treatment of Overdose

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the Investigator should:

1) Contact the Medical Monitor immediately.
2) Closely monitor the participant for any AE/SAE.
3) Document the quantity of the excess of the overdose in the source documents.

8.5 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) are evaluated in this study.

8.9 Immunogenicity Assessments

See Section 8.1.2.

8.10 Medical Resource Utilization and Health Economics

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

9 Statistical Considerations

9.1 Statistical Hypotheses

No hypotheses will be tested. The analyses will be descriptive.

9.2 Sample Size Determination

There are no statistically powered hypotheses in this study thus no formal sample size computation. The number of participants is judged sufficient to provide useful immunogenicity and safety data on the 3 SP0202 formulations, Prevnar 13 and Pneumovax 23.

The sample size was set to approximatively 150 participants per vaccine group and approximatively 75 by age group. Assuming a drop-out rate of approximatively 15%, a total of 128 participants by vaccine group (Per Protocol Analysis Set [PPAS]) are expected.

The expected precision of estimation for quantitative data is as follows (PPAS) - the maximum distance from the log10 mean to the limits of 95% CI is equal to 0.173 for single mean and 0.246 for difference in means of two groups (when the standard deviation is 1).

Standard deviation	N evaluable	Distance between log_{10} mean and 95%CI limits for a single mean	Distance between 2 groups difference in log_{10} means and 95%CI limits	Distance between GMT and 95%CI limits for a single mean	Distance from GMT ratio between 2 groups to 95%CI upper limit
0.5	128	0.087	0.123	1.22	1.33
0.6	128	0.104	0.148	1.27	1.41
0.7	128	0.121	0.172	1.32	1.49
0.8	128	0.139	0.197	1.38	1.57
0.9	128	0.156	0.222	1.43	1.67
1	128	0.173	0.246	1.49	1.76

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Randomized	All participants with data in the CRF
Safety Analysis Set (SafAS)	Participants who have received the study vaccine. All participants will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of randomized participants who received at least 1 dose of the study vaccine and had a valid post-vaccination blood sample result. Participants will be analyzed according to the intervention to which they were randomized.

Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participant did not receive vaccine • Participant received a vaccine other than the one that he / she was randomized to receive • Preparation and / or administration of vaccine was not done as per-protocol • Participant did not provide the post-dose serology sample at V2 in the proper time window or a post-dose serology sample was not drawn • Participant received a protocol-prohibited therapy / medication / vaccine) In addition to the reasons listed above, participants will also be excluded from the PPAS if their Visit 02 / post-vaccination serology sample did not produce a valid test result (ie, results for all antigens are missing). In the event of a local or national immunization program with a pandemic influenza vaccine, participants who receive 1 or more doses of a pandemic influenza vaccine at any time during the study will not be withdrawn from the study.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints.

9.4.1 General Considerations

All analyses will be descriptive.

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 ratio of GMTs / GMCs between 2 groups will be computed from the difference of log 10 transformed means of titers/concentrations using normal approximation.

The 95% CIs of point estimates will be calculated using the exact binomial distribution (Clopper-Pearson method (29)) for proportions.

Generally, no replacement of missing data will be done.

9.4.2 Safety Analyses

Safety analyses will be performed on the SafAS and presented by group and by age group for summary tables (main endpoints). The main parameters will be described with 95% CI. At least number and percentages of participants will be presented after vaccine injection reporting any:

- Immediate unsolicited systemic AEs
- Solicited injection site reactions and solicited systemic reactions occurring within 7 days after the day of injection (D1 to D8) according to presence, time of onset, intensity (Grade 1, Grade 2, or Grade 3), number of days of presence and action taken
- Unsolicited AEs occurring within 30 days after injection by system organ class (SOC) and preferred term (PT), relationship, intensity, time of onset, and duration
- All SAEs occurring throughout the study by SOC and PT, relationship and seriousness criteria
- All AESIs occurring throughout the study by SOC and PT and relationship

No replacement of missing data will be done. Nevertheless, missing relationship will be considered as related at the time of statistical analysis.

9.4.3 Immunogenicity Analyses

All immunogenicity analyses will be performed on the PPAS and presented by group and age group. Additional immunogenicity analyses will be performed on the FAS.

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

- GMT/GMC of serotype specific titers/concentrations
- GM of titers/ concentrations ratio (post- / pre-vaccination)

Differences in terms of ratio of GMTs/GMCs between 2 groups (ie, any SP0202 formulations and Prevnar 13 or Pneumovax 23) post-vaccination will be presented.

Reverse cumulative distribution curves (RCDCs) of individual concentrations/titers will be presented for all serotypes at pre and post-vaccination.

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.

9.4.4 Other Analyses

Any further analyses will be described in the SAP.

9.5 Interim Analyses

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor's internal safety review committee (SMT) which includes safety signal detection at any time during the study. The analyses for SMT will be blinded and descriptive therefore no statistical adjustment is necessary.

A DMC will review continuously related AESIs and related SAEs up the 6-month follow-up. In addition, a first DMC safety analysis on data collected on at least 150 participants up to D31 (30 days after injection) will be conducted in an unblinded manner by an external independent statistician to Sanofi and won't be communicated to the Sponsor. The DMC will also review the unblinded safety data collected up to D31 on all participants. The analyses for this scope will be descriptive so no statistical adjustment is necessary.

A statistical analysis of the safety and immunogenicity objectives up to V02 (Day 31) will be conducted once data on all participants are available and an interim database lock has been conducted. The blind will be broken for the analysis and kept at the Sponsor level until the 6-month follow-up completion. No statistical adjustment is necessary because no hypotheses will be tested. A final analysis will be conducted once the 6-month safety data has been collected and the final database lock has occurred.

If the V01-V02 immunogenicity data release is planned at the time or after the 6-month safety data availability, only one database lock and one analysis including all data may be conducted.

The SAP will describe the planned analyses in greater detail.

9.6 Data Monitoring Committee (DMC)

A DMC has been implemented to oversee the safety data of the SP0202 clinical program and will be utilized throughout this study. The committee will assess the safety data in an unblinded manner. This includes the related AESIs and related SAEs review on ongoing basis, as well as safety profile of each SP0202 formulation prior to database lock.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term "participant" is used throughout this protocol. However, the term "subject" will be used in the CRF in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements.

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Information related to financial disclosure is described in the Investigator's contract.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- 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 participant'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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

The ICF will contain a specific section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each

participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Recruitment Procedures

Before the start of the trial, the Investigator or a sub-investigator will contact an appropriate pool of potential participants and invite them to participate in the study. The site will ensure that any advertisements used to recruit participants (eg, letters, pamphlets, posters) are submitted to Sanofi Pasteur prior to submission to the IEC / IRB for approval.

10.1.4 Data Protection and Future Use of Stored Samples

- All personal data collected related to participants, 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. Data 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.
- Participants race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on African-American population for the Food and Drug Administration).
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data will be used for this study and in support of the whole drug development program for the Investigational Product, including negotiations with payers and publication of results.
- Any unused part of the serum samples will be securely stored by Sanofi Pasteur 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.

  The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health are dedicated for immediate use. In case they are not completely used

up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

In addition, participants 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.

10.1.5 Committees Structure

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor. A blinded review will be performed by the Sponsor during the Safety Management Team (SMT) meeting which includes safety signal detection at any time during the study. Two unblinded reviews by a Data Monitoring Committee (DMC) will also be conducted.

10.1.6 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 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.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Detailed guidance and information are provided in the Operating Guidelines.

10.1.9 Study and Site Start and Closure

Details on which clinical supplies are provided by the Sponsor or the site are described in the Operating Guidelines.

The study start date is considered the date of the first visit planned in the SoA of the first participant.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been either destroyed or returned to the Sponsor, all samples are shipped to the appropriate laboratories, the study-site has all the documents necessary for archiving and a study-site closure visit has been performed. A form will be submitted to IRB to close out the study once all site closeouts have been completed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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 participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

Information related to publication policy is described in the Investigator’s contract.

10.2 Appendix: Clinical Laboratory Tests

A urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) will be performed before vaccination.

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

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions
Adverse Reaction: All noxious and unintended responses to a study intervention related to any dose should be considered adverse reactions (AR).

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

Immediate Event/Reaction:

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

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 study intervention administered.

Systemic AE/AR:

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).

Systemic AEs assessed as related to study intervention are referred as systemic ARs.

Adverse Event of Special Interest (AESI):

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention 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.

Reactogenicity / Solicited Reactions

A solicited reaction is an "expected" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF (eg, injection site pain or headache occurring between the day of vaccination and the next 7 days).

By definition, solicited reactions are considered as being related to the study intervention administered.

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

Unsolicited AE/AR

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and/or onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to study intervention. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other important medical event • Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious. • Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse, new-onset diabetes or autoimmune disease.

Note: *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 participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

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 study intervention (see definition in Section 6 and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

- Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the Investigator only.
  - For SAEs and non-serious AESIs, relationship to study intervention will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
  - For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.

- The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered[a] 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 vaccination
  - Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there is evidence or arguments to suggest a causal relationship
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causal relationship in light of follow-up information and send a SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

[a] Study intervention administered can correspond to either the investigational product or other products when no investigational product is administered at the visit

- If a participant dies during participation in the study or during a recognized follow-up period, when available the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- Adverse events likely to be related to the study intervention, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Details regarding SAE reporting can be found in the Operating Guidelines.

SAE Reporting to the Sponsor via Paper CRF

- The SAE paper CRF can be sent 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@sanofi.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

Safety Emergency Call
If, as per the Investigator's judgment, a participant 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. In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.3.2.

10.3.5 Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.1.1 Solicited AR Intensity Grading Scale

Table 10.1: Solicited injection site reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is 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*	**CRF:** Grade 1: 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. Grade 2: 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. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

MedDRA: Medical Dictionary for Regulatory Activities
* For the subjective reaction of pain, participants 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 10.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Arthralgia	Shivering
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Joint pain	Chills
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Pain in a joint or joints	Sensation of cold

Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	**CRF:** Grade 1: 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.	**CRF:** Grade 1: 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.	**CRF:** Grade 1: 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.	**CRF:** Grade 1: 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.	**CRF:** Grade 1: 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.
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	Grade 2: 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.	Grade 2: 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.	Grade 2: 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.	Grade 2: 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.	Grade 2: 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.

	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions but fever, participants 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:

Participants 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 diary card, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is axillary.

10.3.5.1.2 Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.3.5.1.1).

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

- Grade 1
  - CRF: 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.
  - Diary card: No interference with usual activities.
- Grade 2
  - CRF: 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.
  - Diary card: Some interference with usual activities.
- Grade 3
  - CRF: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - Diary card: Significant; prevents usual activities.

10.4 Appendix: Collection of Pregnancy Information

DEFINITIONS:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1) Premenarchal
2) Premenopausal female with 1 of the following:
   - Documented hysterectomy

- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3) Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

COLLECTION OF PREGNANCY INFORMATION

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information together with the contraceptive method if any will be recorded on the appropriate form and submitted to the Sponsor within 1 month of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date, but will be in accordance with local regulations. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- In case of pregnancy during the primary series and if at least 1 dose of the study vaccine(s) has been administered, the participant will not be discontinued from the study, but no further vaccination will be administered until after delivery (if applicable and still within the study vaccination window). However, the participant will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

10.5 Appendix: Risk-based Approach

ICH E6-R2 guideline for GCP is introducing the « risk-based approach » concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.6 Appendix: Abbreviations

AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
CRF	Case report form
DMC	Data Monitoring Committee
FAS	Full analysis set
FSH	Follicle stimulating hormone
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPV	Global Pharmacovigilance
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committees
IgG	immunoglobulin G
IMP	Investigational Medicinal Product
IPD	invasive pneumococcal disease
IRB	Institutional Review Boards
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
MOPA	multiplex opsonophagocytic assay
NIMP	Non- Investigational Medicinal Product;
PCV	pneumococcal conjugate vaccine
PPAS	Per-protocol analysis set
PPSV	pneumococcal polysaccharide vaccine
PT	preferred term
RMO	Responsible Medical Officer
SAE	Serious adverse events

SafAS	Safety Analysis Set
SAP	Statistical analysis plan
SOC	system organ class
SMT	Safety Management Team
SoA	Schedule of Activities
TBD	to be determined
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
yo	year old

10.7 Appendix: Protocol Amendment History

The Protocol Amendment Rationale for the current amendment is located directly before the Table of Contents.

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12 Sponsor Signature Page

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