NCT04583618

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

Phase II, randomized, observer-blind, controlled, multi-center study
in 750 adults aged 50 to 84 years in the US

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	PSK00009
Development Phase:	Phase II
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, US
Investigational Product(s):	SP0202 - 21-valent Pneumococcal Conjugate Vaccine
Form / Route:	Liquid / Intramuscular (IM)
Indication For This Study:	PCV21 as a single dose in healthy adults aged 50 to 84 years
Version and Date of the SAP core body part:	Version 2.0, 28 April 2021

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List of Abbreviations

Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CI	confidence interval
cLDA	constrained Longitudinal Data Analysis
CRB	case report book [all the case report forms for a participant]
CRF	case report form
CSR	clinical study report
D	day
DC	diary card
DMC	Data Monitoring Committee
dil	dilution
ECL	electro-chemiluminescence assay
FAS	full analysis set
GM	geometric mean
GMC	geometric mean concentration
GMT	geometric mean titer
IgG	immunoglobulin type G
IM	intramuscular
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MOPA	Multiplexed opsonophagocytic killing assay
NA	Not applicable
OPA	opsonophagocytic activity
PCV	pneumococcal conjugate vaccine
PPAS	per-protocol analysis set
PnPS	pneumococcal capsular polysaccharide
PT	preferred term
Q1; Q3	first quartile; third quartile
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan

SD	standard deviation
SMT	Safety Management Team
SOC	system organ class (primary)
TC	Telephone Call
TLF	table(s), listing(s), and figure(s)
ULOQ	upper limit of quantification
V	Visit
VAC	Vaccination

1 Introduction

Sanofi Pasteur is developing a multivalent pneumococcal conjugate vaccine (PCV, henceforth referred to as SP0202) that would extend the protection against pneumococcal disease to serotypes 8, 9N, 10A, 11A, 12F, 15B, 22F, and 33F, in addition to the 13 serotypes included in Prevnar 13® (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). These serotypes have been selected based on recent epidemiological data that showed increasing emergence in North America and in Europe.

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 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.

The SP0202 investigational vaccine is intended to provide protection against invasive and non-invasive diseases caused by the *Streptococcus pneumoniae* serotypes included in the vaccine, in population from infants to elderly.

2 Trial Objectives

Objectives
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
Safety To assess the safety profile of the 3 SP0202 formulations, Prevnar 13, and Pneumovax 23

3 Description of the Overall Trial Design and Plan

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 groups (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:

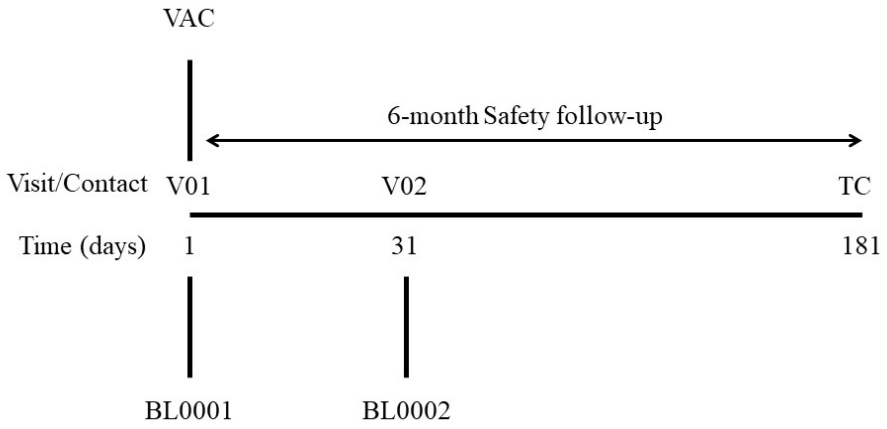
Eligible participants will be randomized in a 1:1:1:1:1 ratio to receive a single intramuscular (IM) injection of either 1 of the 3 SP0202 formulations, Prevnar 13 or Pneumovax 23 at Day (D)01.

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

***Data Monitoring Committee*:** Yes

The graphical design of PSK00009 study is presented in Figure 3.1.

Figure 3.1: Graphical study design



BL: Blood sample
VAC: vaccination
TC: telephone call

Visits procedures are detailed in the Operating Guidelines.

Table 3.1: 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 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 AESIs	X	To be reported at any time during the study		
Collection of 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.

4 Endpoints and Assessment Methods

4.1 Safety Endpoints

The endpoints for the evaluation of safety are:

- 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)

4.1.1 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 of the study protocol.

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.

4.1.2 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 Table 4.1 and Table 4.2.

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

CRB 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 scale (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

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

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Arthralgia	Shivering
Electronic 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 Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°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. 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.	**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.	**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.	**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.	**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: ≥ 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.

Unsolicited Non-serious Adverse Events

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

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

All other unsolicited AEs will be classified according to the intensity scale provided in the protocol Section 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.

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. 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.

4.1.3 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 of the protocol.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

4.1.4 Adverse Events of Special Interest

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

- Anaphylaxis defined as per Brighton collaboration case definition (1)

4.2 Immunogenicity Endpoints and Assessment Methods

The endpoints for the evaluation of immunogenicity are:

- Serotype-specific OPA titers for all pneumococcal serotypes included in the SP0202 formulations, as determined by 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 PnPS-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 PnPS-ECL

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.

4.3 Derived Endpoints: Calculation Methods

4.3.1 Safety

4.3.1.1 Solicited Reactions

4.3.1.1.1 Daily Intensity

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

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

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as "No" and with all daily records missing (Unknown) then all daily intensities will be derived as None.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3. Note: the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement > 0 mm but < 25 mm in adults).

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

4.3.1.1.2 Maximum Overall Intensity

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

4.3.1.1.3 Presence

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

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

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

The time period is displayed as D01-D04, D05-D08, D09 and later.

4.3.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.3.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

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

Time of onset period is displayed as, D01-D04, D05-D08.

4.3.1.1.5 Number of Days of Presence During the Solicited Period

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

4.3.1.1.6 Overall Number of Days of Presence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of presence is derived from the daily intensities and the end date of the reaction after the end of the solicited period. The overall number of days of presence is:

(End date - vaccination date) + (number of days of presence within the solicited period) - length of the solicited period + 1

If the end date is missing or incomplete (contains missing data), the overall number of days of presence will be considered as Missing.

4.3.1.1.7 Ongoing

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

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1.
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it won't be included in the denominator of the ongoing analysis in the safety tables).

4.3.1.2 Unsolicited AEs

4.3.1.2.1 Presence

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

Grade 0 events are not included in safety analysis but are included in separate listings.

4.3.1.2.2 Intensity

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

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement > 0 mm but < 25 mm in adults)

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

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

4.3.1.2.3 Time of Onset

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

Time of Onset = start date of the unsolicited AE - date of the vaccination + 1

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

The unsolicited AEs will be analyzed "Within 30 days" after the vaccination, which corresponds to AEs with a time of onset between 1 and 31 days or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination, so will be included in these tables.

Time of onset period is displayed as D01-D04, D05-D08, D09-D15, D16 or later, and Missing.

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

4.3.1.2.4 Duration

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

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

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

4.3.1.2.5 SAEs

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

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

- Within 30 days after the injection
- During the 6-month follow-up period (ie, from 31 days [from D32] after injection until the last participant contact)
- During the study (ie, all SAEs occurred during the study)

4.3.1.2.6 AESIs

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

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

- Within 30 days after the injection
- During the 6-month follow-up period (ie, from 31 days [from D32] after injection until the last participant contact)
- During the study (ie, all AESIs occurred during the study)

4.3.1.3 Other Safety Endpoints

4.3.1.3.1 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.3.1.3.2 Action Taken

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

4.3.1.3.3 Seriousness

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

4.3.1.3.4 Outcome

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

4.3.1.3.5 Causal Relationship

This information will be summarized as collected in the field "Relationship to Investigational Product". Missing causal relationship will be handled as described in Section 5.5.1.2. Relationship to study procedure for SAE is only presented in the listings.

4.3.1.3.6 AEs Leading to Study Discontinuation

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

In general, the items that are counted are:

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

4.3.2 Immunogenicity

4.3.2.1 Computed Values for Analysis

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

- If a value is < LLOQ, then the computed value is LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then the computed value is the value
- If a value is ≥ ULOQ, then the computed value is ULOQ

4.3.2.2 Thresholds

Generally, if the computed value is ≥ x, then the derived indicator will be “Yes” for that test, otherwise indicator will be "No".

Note: If the computed value is missing, indicator will be missing.

The thresholds are summarized in the table below:

Table 4.3: Immunogenicity thresholds of interest

Endpoints	D01 (V01)	D31 (V02)
Pneumococcal serotype specific functional Ab (OPA)	≥ LLOQ	≥ LLOQ
Pneumococcal serotype specific binding IgG	≥ LLOQ	≥ LLOQ

4.3.2.3 Fold-rise

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

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

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

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

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

If the computed value is ≥ X-fold rises, then the derived ≥ X fold rises indicator will be “Yes” for that test, otherwise ≥ X-fold rises will be "No".

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

4.3.2.4 Seroconversion

Not applicable.

4.3.2.5 Vaccine Response

Not applicable.

4.3.3 Efficacy

Not applicable.

4.3.4 Derived Other Variables

4.3.4.1 Age for Demographics

The age of a participant in the study will be the calendar age in years at the time of inclusion.

4.3.4.2 Study duration

The duration will be computed in days as follows:

Maximum (Visit dates [Visit 01 up to Visit 02], Termination date, Follow-up date, Last contact date) - min (V01 date) + 1

4.3.4.3 Participant Duration

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

Maximum (Visit dates (Visit 01 up to Visit 02), Termination date (if prematurely withdrawn after vaccination), Follow up date, Last contact date) - Visit 01 date + 1.

5 Statistical Considerations

5.1 Statistical Hypotheses

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

5.2 Sample Size Determination

The number of participants is designed to provide immunogenicity and safety data on the 3 SP0202 formulations and on Prevnar 13 and Pneumovax 23 after one injection in healthy adults aged 50 to 84 years.

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

The expected precision of estimation for quantitative data is as follows (PPAS) - the maximum distance from the $\log_{10}$ mean to the limits of 95% CI (confidence interval) 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

5.3 Population for Analyses

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 (serotype specific IgG concentration or serotype specific OPA titer for at least one serotype). 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 V02 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 pneumococcal serotypes for both OPA and IgG 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. As the COVID-19 vaccination campaign has been deployed during the study period, participants who receive 1 or more doses of COVID-19 vaccine during the study period will not be withdrawn from the study.

5.4 Statistical Analyses

5.4.1 General Considerations

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

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

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

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

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

For immunogenicity results, assuming that $\log_{10}$ transformation of the titers / concentrations follows a normal distribution, at first, the mean and the 95% CI will be calculated on $\log_{10}$ (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

CIs of ratio of GMTs / GMCs between 2 groups will be computed from the difference in means of $\log_{10}$ transformed titers/concentrations between 2 groups with normal approximation.

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

5.4.2 Safety Analyses

Safety analyses will be performed on the SafAS and presented by group for all participants and by age group for summary tables (main endpoints). The main parameters will be described with 95% CI. At least the 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 (D01 to D08) 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 SOC and PT, relationship, intensity, time of onset, and duration.
- All SAEs that occur throughout the study by SOC and PT, relationship and seriousness criteria.
- All AESIs that occur throughout the study by SOC and PT and relationship.

5.4.3 Immunogenicity Analyses

The immunogenicity analyses will be performed first on the PPAS and then on the FAS.

The point estimates and their 95% CI of the following parameters will be presented by group for all participants and by age group before and one month post-vaccination for each pneumococcal serotype specific OPA titers and IgG concentrations:

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

In addition, the following analyses will be presented:

- Differences in terms of ratio of GMTs/GMCs between 2 groups (for instance, any SP0202 formulations and Prevnar 13 or Pneumovax 23) and 95% CI at 1-month post-vaccination on all participants and by age group.
- Percentages of participants with titers/concentrations above certain thresholds and achieving several X-fold from pre to post-vaccination.
- Several graphical representations (in a log10 scale) will be used for all serotypes by group for all participants and by age group:
    - RCDCs of individual OPA titers and IgG concentrations at pre and 1-month post-vaccination.
    - Forest plots of GMTs or GMCs at pre and 1-month post-vaccination.
    - Forest plots of GMT/GMC ratio between groups at 1-month post-vaccination.
    - Boxplots of the OPA titers and IgG concentrations at pre and 1-month post-vaccination.

Table 5.2: Summary of statistical analyses for immunogenicity analysis

Endpoint	Visit and Age group	Description
Serotype-specific pneumococcal OPA titer for each of the 21 serotypes	V01 and V02 - all participants V01 and V02 - 50-64 years V01 and V02 - 65-84 years	OPA GMT and 95% CI, corresponding Forest Plot
	V02/V01 - all participants V02/V01 - 50-64 years V02/V01 - 65-84 years	OPA GMT ratio (post/pre) and 95% CI
	V02/V01 - all participants V02/V01 - 50-64 years V02/V01 - 65-84 years	Percentage of participants with titers at V02 ≥ 2/4/8/16-fold rise over V01 and 95% CI and <LLOQ at V01 to ≥LLOQ at V02
	V02 - all participants V02 - 50-64 years V02 - 65-84 years	OPA GMT ratio and 95% CI and corresponding Forest Plot between: - each SP0202 formulation (ie, SP0202-VI/SP0202-IIb, SP0202-VII/SP0202-IIb, SP0202-VII/SP0202-VI) - any SP0202 group and Prevnar 13 or Pneumovax 23 (ie, SP0202-IIb/Prevnar 13, SP0202-VI/Prevnar 13, SP0202-VII/Prevnar 13; SP0202-IIb/Pneumovax 23, SP0202-VI/ Pneumovax 23, SP0202-VII/ Pneumovax 23)
	V01 and V02 - all participants V01 and V02 - 50-64 years V01 and V02 - 65-84 years	OPA titer RCDC
	V01 and V02 - all participants V01 and V02 - 50-64 years V01 and V02 - 65-84 years	OPA titers boxplot
Serotype-specific pneumococcal IgG concentration for each of the 21 serotypes	V01 and V02 - all participants V01 and V02 - 50-64 years V01 and V02 - 65-84 years	IgG GMC and 95% CI, corresponding Forest Plot
	V02/V01 - all participants V02/V01 - 50-64 years V02/V01 - 65-84 years	IgG GMC ratio (post/pre) and 95%CI
	V02/V01 - all participants V02/V01 - 50-64 years V02/V01 - 65-84 years	Percentage of participants with concentrations at V02 ≥ 2/4/8/16-fold rise over V01 and 95% CI and <LLOQ at V01 to ≥LLOQ at V02

	V02 - all participants V02 - 50-64 years V02 - 65-84 years	IgG GMC ratio and 95% CI and corresponding Forest Plot between: - each SP0202 formulation (ie, SP0202-VI/SP0202-IIb, SP0202-VII/SP0202-IIb, SP0202-VII-SP0202-VI) - any SP0202 group and Prevnar 13 or Pneumovax 23 (ie, SP0202-IIb/Prevnar 13, SP0202-VI/Prevnar 13, SP0202-VII/Prevnar 13; SP0202-IIb/Pneumovax 23, SP0202-VI/ Pneumovax 23, SP0202-VII/ Pneumovax 23)
	V01 and V02 - all participants V01 and V02 - 50-64 years V01 and V02 - 65-84 years	IgG concentration RCDC
	V01 and V02 - all participants V01 and V02 - 50-64 years V01 and V02 - 65-84 years	IgG concentration boxplot

5.4.4 Other analyses

COVID-19

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

If more than 10% of randomized participants are impacted by COVID-19, and still evaluable for immunogenicity/safety timepoints, additional analyses in impacted/non-impacted participants will be done on main immunogenicity and safety endpoints.

In addition, in case the 2019-nCOV serostatus is determined for the participants (see Section 4.2 of the protocol), at minimum, results will be presented for tested participants.

Subgroup Immunogenicity analyses

Additional analyses will be done according to gender (two categories: Male, Female), race (two categories: the modality[ies] the most represented versus the pool of the other modalities) and IgG/OPA baseline LLOQ status (ie, <LLOQ or ≥LLOQ) on the main parameters:

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

Baseline adjusted Immunogenicity analyses

In addition to GMT/GMCs ratio between groups, GMTs/GMCs ratio will be computed using constrained Longitudinal Data Analysis (cLDA) model (3).

cLDA will be used to take into account baseline titer/concentration in the model. This approach assumes that the baseline mean values are equal between all groups (reasonable assumption because of the randomization).

Correlation heatmap Immunogenicity analyses

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

All the 'Other analyses' will be conducted in the FAS and provided in Appendix 15 of the CSR.

5.5 Handling of Missing Data and Outliers

5.5.1 Safety

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

5.5.1.1 Immediate

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

5.5.1.2 Causal relationship

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to investigational product at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

5.5.1.3 Intensity

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

5.5.1.4 Start Date and Stop Date

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

similar field. If either the start date or end date is missing or partially missing, the duration will be considered missing.

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

5.5.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

5.5.2 Immunogenicity

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

LLOQ and ULOQ management will be performed as described in Section 4.3.2.1 and Section 4.3.2.3.

5.5.3 Efficacy

Not applicable

5.6 Interim / Preliminary Analysis

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 which includes safety signal detection at any time during the study. The analysis for SMT will be blinded and descriptive therefore no statistical adjustment is necessary.

A DMC (Data Monitoring Committee) will review continuously any related AESIs and related SAEs until the end of 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 will not 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.

5.7 Data Monitoring Committee (DMC)

The committee will assess the safety data in an unblinded manner. This includes the related AESIs and related SAEs review on ongoing basis, the safety analysis of data collected on at least 150 participants up to D31 (30 days after injection) as well as safety profile of each SP0202 formulation with all data up to D31.

5.8 Data Review for Statistical Purposes

No blind review of data will be performed.

5.9 Changes in the Conduct of the Trial or Planned Analyses

No significant change in the conduct of the trial or planned analyses occurred at the time of the SAP writing.

6 References List

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

2 Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72

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