SANOFI PASTEUR

NCT Number: NCT02587520

Safety and Immunogenicity of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Adsorbed (SP0173) in Healthy Adolescents, Adults, and Older Adults

A Phase I/II, randomized, modified double-blind, multi-center, active comparator, dose and formulation ranging, step-down study to assess the safety and immunogenicity of SP0173 in healthy adolescents, adults, and older adults conducted in the US.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	ADC01
Development Phase:	Phase I/II
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product(s):	SP0173 (Tetanus toxoid [T], diphtheria toxoid [d], pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae types 2 and 3 [FIM]).
Form / Route:	Liquid/Intramuscular (IM)
Indication For This Study:	Single dose for individuals ≥ 10 years of age
Version and Date of the SAP core body part:	Version 2.0, 13 December 2016

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List of Abbreviations

Ab	antibody
ADR	adverse drug reaction
AE	adverse event
AR	adverse reaction
BL	blood sample
CDM	Clinical Data Management
CI	confidence interval
CMI	cell mediated immunity
CRF	case report form (electronic)
CTL	Clinical Team Leader
CTM	Clinical Trial Manager
CSR	clinical study report
d	diphtheria
D	day
DC	diary card
dil	dilution
eCRF	electronic case report form
EDC	electronic data capture
EIA	enzyme immunosorbent assay
ELISA	enzyme linked immunosorbent assay
ELS	extensive limb swelling
ESDR	Early Safety Data Review
EU	ELISA or EIA unit
FAS	full analysis set
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
GCP	Good Clinical Practice
GM	geometric mean
GMC	geometric mean concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
ITT	intent-to-treat

IU	international unit
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantitation
LLN	lower limit of normal
MA	memory aid
MAAE	medically-attended adverse events
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
NSAID	non-steroidal anti-inflammatory drug
PC	phone call
PPAS	per-protocol analysis set
PRN	pertactin
PSO	Product Safety Officer
PT	preferred term
Q1; Q2; Q3	first quartile; second quartile (median); third quartile
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SC	screening
SD	standard deviation
SOC	system organ class (primary)
T	tetanus
Tdap	Tetanus, diphtheria, and pertussis vaccine
TLF	table(s), listing(s), and figure(s)
ULOQ	upper limit of quantitation
ULN	upper limit of normal
V	visit
Vac	vaccination
WHO	World Health Organization

1 Introduction

This is a Phase I/II, randomized, modified double-blinded, multicenter, active comparator, dose and formulation ranging, step-down study to assess the safety and immunogenicity of SP0173 (Tetanus Toxoid [T], Reduced Diphtheria Toxoid [d] and Acellular Pertussis Vaccine Adsorbed [ap]) in healthy adolescents, adults, and older adults. The proposed updated tetanus, diphtheria and pertussis (Tdap) vaccine, under evaluation in Study ADC01, will include the same antigenic components as Adacel®. The investigational formulations differ from Adacel® primarily in the amount per dose of pertussis antigens pertussis toxoid (PT), pertactin (PRN), and fimbriae types 2 & 3 (FIM), and/or in the [redacted]. The overall goal is to select a formulation for further clinical development of SP0173 as a combination pertussis vaccine formulation (Tdap) to boost immunity towards the targeted diseases in individuals ≥ 10 years of age.

In Study ADC01, subjects in all groups will be vaccinated with either 1 of the 4 investigational Tdap formulations or a licensed Tdap vaccine (Adacel® or BOOSTRIX®). SP0173 antibody Geometric Mean Concentrations (GMCs) will be evaluated in 1 of 2 ways, depending on subject age. In subjects aged < 65 years, SP0173 antibody GMCs for T, d, and pertussis antigens will be compared with Adacel®. In subjects aged ≥ 65 years, SP0173 antibody GMCs for T and d will be compared with Adacel®, whereas antibody GMCs for pertussis antigens will be compared with historical responses from the Sweden I (for filamentous hemagglutinin [FHA], FIM, and PRN) and M5A10 (for PT) studies. (1)

2 Trial Objectives

2.1 Observational Objectives

Safety / Reactogenicity

- To describe the safety profile of each SP0173 investigational formulation.

Immunogenicity

- To describe the immunogenicity of each SP0173 investigational formulation.

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase I/II, randomized, modified double-blinded, multi-center, active comparator, multiple-formulation, dose ranging, step-down study to assess the safety and immunogenicity of SP0173 in healthy adolescents, adults, and older adults conducted in the United States (US.)..

Subjects' age groups are defined as follows:

- Adolescents: aged 10 to 18 years.
- Adults: aged 19 to 64 years.
- Older Adults: aged ≥ 65 years.

The planned sample size is 1350 subjects (450 subjects per age group). Within each age group subjects will be randomized in equal proportion to receive a single dose of SP0173 (1 of 4 formulations), Adacel®, or BOOSTRIX®.

Subjects will be monitored for immediate unsolicited systemic AEs for 30 minutes after vaccination. Solicited reactions (injection site and systemic) will be collected from Day (D)0 to D7 post-vaccination. Unsolicited AEs will be collected from Visit (V)1 (D0) to V02 (D30 to D44) and SAEs will be collected throughout the study period from D0 through D180 after vaccination. Medically-attended adverse events (MAAEs) will be collected throughout the study from V01(D0) to V02(D30-D44) as part of the collection of unsolicited AE information and from V02 to the end of the 6-month (D180) follow-up as MAAEs. An MAAE that occurs within the study period but meets the definition of an SAE should be reported as an SAE.

Table 3.1: Study groups and vaccine formulations

[redacted]

3.2 Trial Plan

A schedule of assessments and study vaccinations is provided in the Table of Study Procedures (see Table 3.2).

Table 3.2: Study procedures

Table of Study Procedures

Phase I/II Study, 2 Visits, 1 Vaccination, 2 Telephone Calls 2 Blood Samples, 180-Days Duration Per Subject

Visit (V)/Contact	Visit 1 (V01)	Telephone Contact 1(TC1)	Visit 2 (V02)	Telephone Contact 2 (TC2)
Study timelines (days)	D0	D8	D30	D180
Time windows (days)		[+3 Days]	[+ 14 Days][*]	[+14 days]
Informed consent form/Assent form (if applicable[†])	X			
CMI informed consent addendum form, as applicable	X			
Inclusion/exclusion criteria	X			
Temperature	X			
Collection of demographic data	X			
Urine pregnancy test (if applicable)[‡]	X			
Verbal medical and vaccination history	X			
Physical examination[§]	X			
Collection of Concomitant Therapy	X			
Measure circumference of both arms[††]	X			
Randomization/allocation of subject number	X			
Blood sampling (BL), approximately 10–20 mL[‡‡]	BL1		BL2	
Vaccination	X			
Immediate surveillance (30 min)	X			
Diary card provided	X			
Telephone contact[§§]		X		
Diary card collected and reviewed			X	
Collection of solicited injection site and systemic reactions			X	
Recording of unsolicited AEs	D0 to V02			
Memory aid provided[***]			X	
Recording of MAAEs[†††]			V02 to TC2	
Recording of SAEs	To be reported at any time during the study			
Follow-up telephone call[‡‡‡]				X
Completion of 6-month follow-up				X

[*]For subjects in the CMI subset, the window will be [+ 7 Days].
[†]Age of majority to follow state regulations
[‡]For women of childbearing potential. The urine pregnancy test must be performed before vaccination. The pregnancy test must be negative for enrollment.
[§]Targeted physical examination based on medical history. Temperature needs to be measured and recorded in the source documents.
[††]If the subject develops a Grade 3 solicited injection site (including ELS) or systemic reaction, the subject or subject's parent/guardian is required to contact the site immediately. The site must attempt for the subject to be seen at the study site within 24 hours to assess the extent of the reaction.
[‡‡]Collection of the baseline blood sample (BL1) before vaccination, approximately 10 mL. An additional 10 mL will be collected for the CMI subgroup at each time point.
[§§]This call to be made 8 to 10 days after the vaccination at V01. If D8 (+3 days) falls on a weekend or a holiday, the telephone call may be made on the following working day. During this call the staff will determine whether the subject experienced any SAE, Grade 3 solicited adverse reactions (including ELS) not yet reported, remind the subject or subject's parent/guardian to continue to use the DC up to V02 and to bring the DC to the study center at V02, and will confirm the date and time of V02.
[***]The MA is used for recording any AEs between V02 and TC2.
[†††]An MAAE that occurs between V01 and V02 will be recorded as unsolicited AEs.
[‡‡‡]Staff will contact the subject or subject's parent/guardian by telephone at 180 days (+14 days) after vaccination at V01 to identify the occurrence of any MAAEs and unreported SAEs for the period between V02 and TC2.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

There are no primary objectives in this study.

4.2 Secondary Endpoints and Assessment Methods

There are no secondary objectives in this study.

4.3 Observational Endpoints and Assessment Methods

4.3.1 Safety

4.3.1.1 Safety Definitions

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

Adverse Event (AE):

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

Therefore an AE may be:

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

All AEs include serious and non-serious AEs.

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

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

Serious Adverse Event (SAE):

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

An SAE is any untoward medical occurrence that at any dose

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

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

[b] All medical events leading to hospitalizations will be recorded and reported as Serious Adverse Events, with the exception of: hospitalization planned before inclusion into the study or out-patient treatment with no hospitalization.

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

[d] Medical and 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 subject or may require intervention to prevent one of the

Adverse Reaction:

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

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

Unexpected Adverse Reaction (UAR):

An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

The following additional definitions are used by Sanofi Pasteur:

Solicited Reaction:

A solicited reaction is an event that is prelisted in the CRF**.** The assessment of these AEs post-vaccination is mandatory. A solicited reaction is defined by a combination of:

- Symptom and
- Onset post-vaccination

e.g., injection site pain between D0 and D7 post-vaccination, or headache between D0 and D7.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRF and considered as related to vaccination.

Unsolicited AE/AR:

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRF in terms of diagnosis and/or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D7 is a solicited reaction (i.e., prelisted in the CRF), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE.

An unsolicited non-serious AE is an unsolicited AE excluding SAEs.

Injection Site Reaction:

An injection site reaction[a] is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions.

other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new onset diabetes, or autoimmune disease.

[a] All injection site AEs are considered to be related to vaccination and are therefore all *injection site reactions*.

Systemic AE:

Systemic AEs are all AEs that are not injection 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 site, e.g., erythema that is localized but that is not at the injection site.

Medically Attended Adverse Events (MAAEs)

An MAAE is defined, for the purpose of this study, as a new onset of a condition that prompts the subject or subject's parent/guardian to seek unplanned medical advice at a physician's office or Emergency Department. This definition excludes pre-planned medical office visits for routine pediatric check-ups or follow-up visits of chronic conditions with an onset prior to entry in the study. Physician contact made over the phone or by email will be considered a physician office visit for the purpose of MAAE collection.

4.3.1.2 Safety Endpoints

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, action taken, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited (prelisted in the subject DC and eCRF) injection site reactions and systemic reactions occurring through D7 after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs occurring from vaccination through 30 days after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, seriousness criteria, relationship to vaccination, and outcome of SAEs from V01 to 6-month follow-up for all groups after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, seriousness criteria, relationship to vaccination, and outcome of MAAEs from V02 to the 6-month follow-up for all groups after vaccination.

4.3.1.3 Safety Assessment Methods

At V02, the Investigator or a delegate will ask the subject or subject's parent or guardian about any solicited reactions and unsolicited AEs recorded in the DC, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the eCRF according to the instructions provided by the Sponsor.

4.3.1.3.1 Immediate Post-Vaccination Surveillance Period

Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination surveillance should be documented in the source document. Any AE that

occurs during this period will be noted on the source document and recorded in the eCRF, as follows:

- Any unsolicited systemic AE occurring during the first 30 minutes post-vaccination will be recorded on the eCRF as immediate unsolicited systemic AE.
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded and analyzed as starting on the day of vaccination.
- Any SAE occurring during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor.

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

After vaccination, subjects or subjects' parents/guardians will be provided with a safety DC, a digital thermometer, measuring tape and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the DC on the day of vaccination and for the next 7 days (i.e., D0 to D7) until resolution:

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

The action taken by the subject or the subject's parents/guardians to treat any **solicited reactions** will be classified in the eCRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

4: Hospitalization (inpatient)

Subjects or subjects' parents/guardians will be contacted by telephone 8 days after vaccination to identify the occurrence of any SAE, Grade 3 solicited adverse reactions (including ELS) not yet reported and to remind them to record all safety information in the DC up to V02 and to bring the DC back to V02. The date of the appointment for V02 will be confirmed.

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

Table 4.1 and Table 4.2 present, respectively, the injection site reactions and systemic reactions that are prelisted in the DCs and CRF, together with the intensity scales.

Table 4.1: 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	Upper limb edema	Extensive swelling of the vaccinated limb
Diary card term	Pain*	Redness*	Swelling*	Change in limb circumference*	Extensive limb swelling*
Definition		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	Increase in limb circumference compared to pre-vaccination measurement of the same arm	Swelling of the injected limb including the adjacent joint (i.e., elbow and/or shoulder) as compared to baseline.
Intensity scale*	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	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	Grade 1: > 0 to < 25 mm increase over pre-vaccination measurement Grade 2: ≥ 25 to < 50 mm increase over pre-vaccination measurement Grade 3: ≥ 50 mm increase over pre-vaccination measurement	Not applicable‡

* If any Grade 3 solicited injection site reaction (including ELS) is present, the subject or subject's parent/guardian will be instructed to call the site immediately.

† For the subjective reaction of pain, subjects or subject's parent/guardian will record the intensity level (Grade 1, 2, or 3) in the DC. For the measurable reactions of redness, limb circumference, and swelling, they will record just the size of the reaction, and the classification, as Grade 1, 2, or 3 will be assigned by the statistician.

‡ By convention, ELS is considered as severe.

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

CRF term (MedDRA lowest level term [LLT])	**Fever**	**Headache**	**Malaise**	**Myalgia**
Diary card term	Temperature*	Headache*	Feeling unwell*	Muscle aches and pains*
Definition	Elevation of temperature to ≥ 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.
Intensity scale**	Grade 1: ≥ 100.4°F to ≤ 101.1°F Grade 2: ≥ 101.2°F to ≤ 102.0°F Grade 3: ≥ 102.1°F	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity		

*If any Grade 3 solicited systemic reaction is present, the subject or subject's parent/guardian will be instructed to call the site immediately.

**For all reactions but fever, subjects or subject's parent/guardian will record the intensity level (Grade 1, 2, or 3) in the DC. 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.

Important notes for the accurate assessment of temperature:

Subjects or subjects' parents/guardians are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the DC, and the highest temperature will be recorded by the site in the CRF. The preferred route for measuring body temperature in this trial is the oral route. Pre-vaccination temperature is also systematically collected by the investigator in the source document. Tympanic thermometers must not be used.

Important notes for the accurate measurement of limb circumference:

Study personnel will instruct the subject (or subject and their parent/guardian) how to perform and record the limb circumference measurements using the measuring tape and measuring horizontally at the level of the axilla. The subject will be requested, under the supervision of the study staff, to perform the baseline measurement of both arms with the staff, immediately before immunization (baseline measurement) at V01. The circumference of both arms will be recorded in the source document and that of the vaccinated arm will be transcribed in the subject's DC. The measurement of the vaccinated arm will be recorded daily by the subject or subject's parent/guardian in the DC.

If the subject develops Grade 3 change in limb circumference (≥ 50 mm over pre-vaccination measurement at baseline) or ELS[6] (soft tissue swelling that occurs post-vaccination and extends from the injection site to involve an adjacent joint [e.g. the elbow, shoulder joint, or both]) which occur during the 7-day period after vaccination, the subject (or parent/guardian) is required to contact the site immediately. The site must attempt to arrange for the subject to be seen at the study site within 24 hours to assess the extent of the reaction. The subject (or parent/guardian) is to be instructed to take measurements of the vaccinated limb circumference and record in the DC until the swelling is resolved (See Operating Guidelines for details).

4.3.1.3.3 Unsolicited Non-serious Adverse Events From D0 to V02 After Vaccination

In addition to recording solicited reactions, subjects or subjects' parents/guardians will be instructed to record any other medical events that may occur between V01 and V02. Space will be provided in the DC for this purpose. For each unsolicited non-serious AE, the following information is to be recorded:

- Start and stop dates[7]
- Intensity of the event:
    - For measurable unsolicited non-serious AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see Table 4.1 andTable 4.2).

[6] Regardless of the arm circumference measurements and differences, if in the subject's or subject and their parent/guardian opinion the subject develops ELS of the vaccinated arm during the 7 day period after vaccination, the subject or subject and their parent/guardian is required to contact the site immediately on the same day the ELS is observed

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

- Other unsolicited non-serious AEs will be classified according to the following intensity scale:
  - Grade 1: No interference with activity
  - Grade 2: Some interference with activity
  - Grade 3: Significant; prevents daily activity
- Action taken for each AE, if any (e.g., medication)

The action taken by the subjects or subjects' parents/guardians to treat any **unsolicited AEs** will be classified in the eCRF using the following scale:

0: None

1: Medication (self-medication with an existing prescription or over-the-counter medication)

2: Health care provider contact (no new medication prescribed)

3: Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication, either an over-the-counter medication or one requiring a written prescription)

- Whether the AE led to discontinuation
- Whether the AE was related to vaccination (for unsolicited systemic AEs)

4.3.1.3.4 Serious Adverse Events

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

Any SAE occurring at any time during the trial will be reported by the Investigator through the EDC system and according to the completion guidelines provided by the Sponsor. All information concerning the SAE is to be reported, either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). The Investigator will assess the causal relationship between the SAE and the investigational product as either "Not related" or "Related", as described in Section 4.3.1.3.7.

4.3.1.3.5 Adverse Events of Special Interest

No Adverse Events of Special Interest will be assessed in this study.

4.3.1.3.6 Medically Attended Adverse Events

MAAEs that occur from V01 (D0) to V02 will be recorded as unsolicited AEs on the DC as part of the unsolicited AEs collected for this post-vaccination period. MAAEs that occur from V02 to the long-term safety phone call at approximately 6 months after vaccination will be recorded as such in the MA. An MAAE that occurs within the study but meets the definition of an SAE should be reported only on the SAE reporting form.

4.3.1.3.7 Assessment of Causality

The Investigator will assess the ***causal relationship*** between each unsolicited systemic AE and vaccination as either not related or related, based on the following definitions[8]:

0: Not related – The AE is clearly / most probably caused by other etiologies such as subject's 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 (screening phase, if applicable)

1: Related – There is a "reasonable possibility" that the AE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship

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

AEs likely to be related to the product, whether serious or not, that persist at the end of the trial will be followed up by the Investigator until their complete disappearance or the stabilization of the subject's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event.

4.3.2 Immunogenicity

4.3.2.1 Immunogenicity Endpoints

- Anti-pertussis (PT, FHA, PRN, and FIM) antibody concentrations pre- and post-vaccination measured by enzyme-linked immunsorbent assay (ELISA)
- Anti-diphtheria antitoxin concentration pre- and post-vaccination assessed by toxin neutralization assay
- Anti-tetanus antitoxin concentration pre- and post-vaccination measured by ELISA

4.3.2.2 Immunogenicity Assessment Methods

Anti-Bordetella pertussis Antibodies

Assays will be performed by ELISA at Sanofi Pasteur. Purified PT, FHA, PRN, or FIM 2&3 antigen is adsorbed to the wells of a microtiter plate. Diluted serum samples (test samples, reference standards, and quality controls) are incubated in the wells. Specific antibodies in the serum samples bind to the immobilized antigen to form antigen-antibody complexes. Unbound antibodies are washed from the wells, and enzyme-conjugated anti-human immunoglobulin (IgG) is added. The enzyme conjugate binds to the antigen-antibody complex. Excess conjugate is washed away and a specific colorimetric substrate is added. Bound enzyme catalyzes a hydrolytic reaction causing color development. The intensity of the generated color is proportional to the amount of specific antibody bound to the wells. The results are read on a spectrophotometer

[8] ICH Guidelines, Clinical Safety Data Management E2A

(ELISA plate reader). An in house reference standard serum assayed on each plate is used to calculate the amount of specific PT, FHA, PRN, or FIM 2&3 antibody in the test samples in ELISA units per milliliter (EU/mL) by comparison to the reference standard curves. The lower limit of quantitation (LLOQ) for the anti-PT, PRN, and FIM ELISA is 4 EU/mL and the LLOQ for the anti-FHA ELISA is 3 EU/mL.

Antibodies to Tetanus Toxin

Assays will be performed by ELISA at Sanofi Pasteur. Purified tetanus toxoid is adsorbed to the wells of a microtiter plate. Diluted serum samples (test samples, reference standard, and quality control) are incubated in the wells. Specific antibodies in the serum samples bind to the immobilized antigen. Unbound antibodies are washed from the wells, and enzyme-conjugated anti-human immunoglobulin (IgG) is added. The enzyme conjugate binds to the antigen-antibody complex. Excess conjugate is washed away and a specific colorimetric substrate is added. Bound enzyme catalyzes a hydrolytic reaction, which caused color development. The intensity of the generated color is proportional to the amount of specific antibody bound to the wells. The results are read on a spectrophotometer (ELISA plate reader). A reference standard assayed on each plate, WHO human standard lot TE3, is used to calculate the amount of specific anti-tetanus antibody in the unitage assigned by the reference standard (IU/mL of serum). The LLOQ for the anti-tetanus ELISA is 0.01 IU/mL.

Antibodies to Diphtheria Toxin

Assays are performed by a toxin neutralization test at Sanofi Pasteur. Serial dilutions of human sera are mixed with diphtheria challenge toxin and incubated with Vero cells that are sensitive to the toxin. Neutralizing antibodies specific to diphtheria toxin contained in the serum samples bind to and neutralize the toxin. The neutralized toxin does not affect cellular viability, therefore the cultured cells continue to metabolize and release carbon dioxide (CO_2), reducing the pH of the culture medium. Cell survival correlates with the change in the color of the pH indicator (phenol red to yellow at $pH \leq 7.0$) contained in the medium. In the absence of neutralizing antibodies, the challenge toxin reduces cellular metabolism and CO_2 production, therefore the pH does not decrease and a color change is not detected. The LLOQ is 0.005 IU/mL.

4.3.3 Efficacy

No clinical efficacy data will be obtained in the trial.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 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.

Note: all instances of extensive limb swelling will be considered a Grade 3 reaction.

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

1) Solicited reactions (except Fever/Pyrexia) with an investigator presence recorded as "No" and with all daily records missing 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 (e.g., 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.

4.4.1.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Presence

Presence is derived from the maximum overall intensity on the period considered:

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

Subjects 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.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., 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 occurrence.

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

4.4.1.1.6 Overall Number of Days of Occurrence

Not applicable.

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 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. Note the intensity could be considered None (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

If the last daily intensity of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

4.4.1.2 Unsolicited Non-serious AEs

4.4.1.2.1 Intensity

Intensity for unsolicited non-serious AE will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

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

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

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

Note: If a measurable unsolicited non-serious event not matching solicited reactions does not have an intensity reported in the clinical database, then the statistician should work with the clinical team to determine intensity and include the scales in this section. If no scales can be determined, then the intensity should remain missing.

4.4.1.2.2 Last Vaccination

Not applicable, as there is only one vaccination.

4.4.1.2.3 Time of Onset

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

- start date of the unsolicited non-serious AE minus date of previous vaccination

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

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

Note: Unsolicited non-serious AE that occurred before vaccination (negative time of onset) or with a time of onset will not be included in analysis, but will be listed separately.

4.4.1.2.4 Duration

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

- stop date of unsolicited non-serious AE - start date of unsolicited non-serious AE + 1.

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

4.4.1.3 SAEs

4.4.1.3.1 Last Vaccination

Not applicable, as there is only one vaccination.

4.4.1.3.2 Time of Onset

Time of onset will be computed using the same methodology than for unsolicited non-serious AEs described in Section 4.4.1.2.3.

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

- Within 7 days after vaccine injection
- Within 30 days after vaccine injection
- During the 6-month follow-up period (i.e., from V02 until the last subject contact)
- During the study (i.e., all SAEs occurred during the study)

An SAE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: SAEs that occurred before vaccination (negative time of onset) will not be included in analysis, but will be listed separately.

4.4.1.3.3 Duration

Duration will be computed using the same methodology than for unsolicited non-serious AEs described in Section 4.4.1.2.4.

4.4.2 Immunogenicity

4.4.2.1 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, the following computational rule is applied to the values provided in the clinical database for each BL drawn:

- 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

4.4.2.2 Seroprotection

Generally, If the computed value is ≥ x, then the derived seroprotection indicator will be “Yes” for that test, otherwise seroprotection will be "No". Note: If the computed value is missing, seroprotection will be missing.

For diphtheria, seroprotection is defined as:

- Anti-diphtheria antitoxin concentration ≥ 0.01, ≥ 0.10, and ≥ 1.0 IU/mL (International Unit)

For tetanus, seroprotection is defined as:

- Anti-tetanus antitoxin concentration ≥ 0.01, ≥ 0.10, and ≥ 1.0 IU/mL

4.4.2.3 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-baseline computed values and is computed as follows. Generally, for extreme values, this algorithm minimizes the numerator and maximizes 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 ≥4, then the derived ≥4-fold rises indicator will be “Yes” for that test, otherwise ≥4-fold rises will be "No".

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

4.4.2.4 Seroconversion

Not applicable

4.4.2.5 Booster response

The criterion for demonstrating a pertussis booster response is as follows:

- If the pre-booster vaccination concentration is < 4xLLOQ, then the post-booster vaccination concentration is ≥ 4x the pre-booster concentration*
- If the pre-booster vaccination concentration is ≥ 4xLLOQ, then the post-booster vaccination concentration is ≥ 2x the pre-booster concentration.

  * Pre-booster vaccination concentrations < LLOQ will be converted to LLOQ for purposes of calculating this booster response.

An equivalent definition for ease of programming:

- If the pre-booster vaccination concentration is missing or No Result (NR) or if the post-booster vaccination concentration is missing or NR, then the booster response is missing
- Else if the pre-booster vaccination concentration is < 4xLLOQ, then the booster response will be demonstrated if there is a 4-fold rise (post-/pre- vaccination ≥ 4)
- Else if the pre-booster vaccination concentration is ≥ 4xLLOQ, then the booster response will be demonstrated if there is a 2-fold rise (post-/pre- vaccination ≥ 2)

For diphtheria and tetanus the criteria for demonstrating a booster response are as follows:

- Subjects whose pre-vaccination antibody concentrations are < 0.1 IU/mL will demonstrate the booster response if they have a post-vaccination level ≥ 0.4 IU/mL
- Subjects whose pre-vaccination antibody concentrations are ≥ 0.1 IU/mL but < 2.0 IU/mL will demonstrate the booster response if they have a 4-fold rise (i.e., post-/pre-vaccination ≥ 4)
- Subjects whose pre-vaccination antibody concentrations are ≥ 2.0 IU/mL, will demonstrate the booster response if they have a 2-fold response (i.e., post-/pre-vaccination ≥ 2)

An equivalent definition for ease of programming:

- If the pre-vaccination antibody concentration is missing or No Result (NR) or if the post-booster vaccination concentration is missing or NR, then the booster response is missing
- Else if the pre-vaccination antibody concentration is < 0.1 IU/mL, then the booster response will be demonstrated if the post-vaccination level ≥ 0.4 IU/mL
- Else if 0.1 IU/mL ≤ pre-vaccination antibody concentration < 2.0 IU/mL, then the booster response will be demonstrated if there is a 4-fold rise (i.e., post-/pre-vaccination ≥ 4)
- Else if the pre-vaccination antibody concentration is ≥ 2.0 IU/mL, then the booster response will be demonstrated if there is a 2-fold rise (i.e., post-/pre-vaccination ≥ 2)

4.4.3 Efficacy

Not applicable

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

Ages of subjects will be calculated as Age (years) = (date of vaccination – date of birth +1)/365.25

4.4.4.2 Duration of a Subject in the Study

The duration of a subject in the study is computed as follows: Maximum (date of last visit, date of term form) – (date of V01) +1.

The duration of a subject in the study including follow-up is computed as follows: Maximum (date of last visit, date of term form, last date of follow-up contact) – (date of V01) +1.

4.4.4.3 Duration of the Study

The duration of the study (until last visit) is computed as follows: Maximum of all subjects (date of last visit, date of termination form) – minimum for all subjects (date of V01) +1.

The duration of the study (including follow-up) is computed as follows: Maximum of all subjects (date of last visit, date of termination form, date of last follow-up contact) – minimum for all subjects (date of V01) +1

4.4.4.4 Subject Duration

The duration of a subject participation in the study is computed as follows:

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

4.4.4.5 MAAEs from V01 to V02

MAAEs that occur from V01 to V02 will be recorded as unsolicited AEs on the diary card as part of all unsolicited AEs collected for this post-vaccination period. The unsolicited AEs that have action taken categories 2 (health care provider contact) or 3 (Health care contact + Medication) will be summarized and presented as MAAEs which occurred from V01 to V02.

5 Statistical Methods and Determination of Sample Size

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

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

For descriptive purposes, the statistics will be presented as following:

Categorical variables: number and percentage of subjects in each category will be summarized.
Age: number of observations (n), mean, and standard deviation (SD).

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

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

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

There are no primary objectives in this trial.

5.1.2 Hypotheses and Statistical Methods for Secondary Objective(s)

There are no secondary objectives in this trial.

5.1.3 Statistical Methods for Observational Objective(s)

5.1.3.1 Hypothesis

No hypotheses will be tested. Descriptive statistics will be presented.

5.1.3.2 Statistical Methods

5.1.3.2.1 Demographics and disposition

Summaries of the recruitment and baseline demographic characteristics of the study subjects will be presented. The number of subjects enrolled and their age at enrollment (mean, median, and minimum and maximum), sex, and ethnic origin will be summarized, along with the number and description of protocol violations.

5.1.3.2.2 Safety

The number and percentage of subjects reporting any solicited injection site reactions and solicited systemic reactions will be summarized by study group, intensity (Grade 1, Grade 2, and Grade 3), and period (D0 to D3, D4 to D7, and D0 to D7 after vaccination) for each reaction term. For a time period in which more than 1 intensity was recorded, the highest intensity will be used. Exact (Clopper-Pearson) 2-sided 95% confidence intervals (CIs) will be calculated for the percentages.

Immediate reactions, unsolicited AEs (including MAAEs), and SAEs will be coded and presented by MedDRA preferred term and system organ class (SOC). The number and percentage of subjects reporting safety findings will be summarized by study group for each preferred term, and SOC that has at least 1 report, as well as by relationship to study vaccine. SAEs will be tabulated separately from D0 through the end of the 6 month follow-up. Unsolicited AEs representing a change in the health status of the subject will be presented from D0 through D30. MAAEs will be presented from V01 through V02 through the end of the 6-month follow-up period.

Descriptive statistics will include, but not be limited to:

Table 5.1: Statistical analyses for safety observational objective

Safety Events	Time and Group	Description
Immediate unsolicited systemic AE	Within 30 minutes after injection for all subjects in Groups 1 - 6 at D0	Percentage of subjects that have the event, MedDRA terms, intensity, relationship to vaccine, study discontinuation, duration
Extensive limb swelling	Up to 7 days after D0 for all subjects in Groups 1 – 6	Percentage of subjects that have the event
Solicited injection site reactions	Up to 7 days after D0 for all subjects in Groups 1 – 6	Percentage of subjects that have the event, time of onset, duration, intensity, action taken, study discontinuation, number of days of occurrence
Solicited systemic reactions	Up to 7 days after D0 for all subjects in Groups 1 – 6	
Unsolicited AE	Up to 7 days after D0 for all subjects in Groups 1 – 6 From D0 to D30 for all subjects in Groups 1 – 6	Percentage of subjects that have the event, MedDRA terms, time of onset, duration, intensity, relationship, action taken, study discontinuation
SAE	Up to 7 days after D0 for all subjects in Groups 1 – 6 From D0 to D30 for all subjects in Groups 1 – 6 From D31 to 6-month follow-up contact for all subjects in Groups 1 – 6 Up to 6-month follow-up contact after D0 for all subjects in Groups 1 – 6	Percentage of subjects that have the event, MedDRA terms, time of onset, duration, relationship, seriousness criteria, outcome, study discontinuation
MAAE	From V01 to V02 for all subjects in Groups 1 - 6 (as unsolicited AE) From V02 to 6-month follow-up contact for all subjects in Groups 1 - 6	Percentage of subjects that have the event, MedDRA terms, time of onset, duration, intensity, relationship, action taken, outcome, study discontinuation

5.1.3.2.3 Immunogenicity

Descriptive statistics will include, but not be limited to:

Table 5.2: Statistical analyses for immunogenicity observational objectives

Antigen	Time and Group	Description
Tetanus and diphtheria	At D0 and D30 for all subjects in Groups 1 - 6	GMC and 95% CI (unadjusted and adjusted)
		RCDC
		Percentage of subjects with concentration ≥ 0.01 IU/mL and 95% CI
		Percentage of subjects with concentration ≥ 0.10 IU/mL and 95% CI
		Percentage of subjects with concentration ≥ 1.0 IU/mL and 95% CI
		Percentage of subjects with booster response from D0 to D30 and 95% CI
PT, FHA, PRN and FIM	At D0 and D30 for all subjects in Groups 1 - 6	GMC and 95% CI (unadjusted and adjusted)
		RCDC
		Percentage of subjects with booster response from D0 to D30 and 95% CI ()

- ***For pertussis, immunogenicity of SP0173 investigational formulations will be assessed by comparison of post-vaccination GMCs to the following:***
- In adolescents and adults:
    - booster response rates and
    - antibody GMCs
    - after a single Adacel® dose
- In older adults:
    - booster response rates to pre-determined criteria (must be greater than 60%)
    - antibody GMCs compared to that after 3 doses of DTaP (Daptacel®) vaccine given to infants in the historical Sweden I efficacy trial (for FHA, PRN and FIM) or after 4 doses of Daptacel vaccine given to per-protocol subjects in Sanofi Pasteur Study M5A10 (for PT)

For sera obtained after vaccination, in addition to unadjusted GMCs, GMCs will be computed using analysis of covariance to adjust for baseline disparities, i.e., through an ANCOVA model using the pre-vaccination concentration as a covariate for adjustment in order to account for the variability linked to the baseline concentration and to provide a ”change from baseline” analysis.

Note booster response rates partially adjust for individual and population differences in pre-vaccination antibody concentrations, so no further baseline adjustment is necessary.

For ***diphtheria and tetanus***, immunogenicity of the investigational formulations in each of the age groups will be assessed by comparison to booster response rates, seroprotection rates and post-vaccination GMCs after a single Adacel® dose.

5.1.4 Complementary Output

Additional analyses for subjects aged 65 to 74 years and subjects aged ≥ 75 years may be provided in Appendix 15 of the CSR.

5.2 Analysis Sets

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

5.2.1 Per-Protocol Analysis Set

The per-protocol analysis set (PPAS) is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he/she was randomized to receive
- Preparation and/or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window (this is a standard criterion that refers to the interval between vaccines, but does not apply in this study, as there is only one vaccine, unless one applies it to being assigned to the correct stratum).
- Subject did not provide post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited medication
- Subject's post-dose serology sample did not produce a valid test result for all antigens, i.e., a subject would have to have no post-dose antigens with a valid test result to be excluded from PPAS for this criterion.

5.2.2 Full Analysis Set

The full analysis set (FAS) is defined as the subset of randomized subjects who received at least one dose of the study vaccine. Subjects will be analyzed according to the vaccine to which they were randomized. If a subject receives only vaccines received out of the protocol design, his data will be excluded from the analysis (and listed separately).

5.2.3 Safety Analysis Set

The Safety Analysis Set (SafAS) is defined as those subjects who have received study vaccine. All subjects 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).

5.2.4 Populations Used in Analyses

The primary immunogenicity analyses will be performed on the FAS, and will be confirmed on the PPAS. In the FAS, subjects will be analyzed by the vaccine group to which they were randomized.

The SafAS will be performed on the safety analysis set.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

No replacement will be done. All subjects with safety data and all safety data recorded in the eCRFs will be included in the safety analyses.

In all subject listings, partial and missing data will be clearly indicated as missing.

5.3.1.1 Immediate

For unsolicited non-serious 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.

For SAEs, missing or partially missing elapsed time from last vaccination recorded if within 24 hours will be assumed to have occurred after the 30-minute surveillance period and will not be imputed. Such SAEs will not be considered as immediate.

5.3.1.2 Causality

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.1.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited non-serious AEs 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 collected.

Since SAEs are not collected by visit, though missing or partially missing start dates will not be imputed, logic will be applied to determine whether the event started between D0 to D30 or between D31 to 6-month follow-up contact.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.3.2 Immunogenicity

For the calculation of GMCs and seroprotection, any pre-vaccination or post-vaccination titer reported as < LLOQ will be converted to a value of 0.5 LLOQ. For the calculation of 4-fold rise, any pre-vaccination value reported as < LLOQ will be converted to LLOQ, and any post-vaccination titer 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 4-fold rise is defined as 1. Any titer reported as > ULOQ (upper limit of quantitation) will be converted to ULOQ.

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

5.3.3 Efficacy

No efficacy data was collected for this study.

5.4 Interim / Preliminary Analysis

No interim analyses are planned. An initial internal safety review (ESDR) for this study is planned when all adult subjects have been vaccinated and have provided safety data for V01 through V02 post-vaccination, using the data collection methods described in the protocol. The safety data collected will be entered into the electronic case report forms (eCRFs), and will be summarized and reviewed in a per-group partially blinded (group unblinded) fashion by the Sponsor. It is understood that this review will be based on preliminary data that have not been subject to validation and database lock. No statistical adjustment is necessary because no hypotheses will be tested.

5.5 Determination of Sample Size and Power Calculation

Although there are no statistically powered hypotheses in this study, the overall study cohort (N=1350) will provide a probability of approximately 93% of observing any AE with a true incidence of 0.2%. For each formulation (N=225), there is a probability of approximately 95% of

observing any AE with a true incidence of 1.3%, and a probability of approximately 36% of observing any AE with a true incidence of 0.2%.

Assuming a drop-out rate of approximately 10%, a total of 67 evaluable subjects per group is anticipated.

5.6 Data Review for Statistical Purposes

A blind review of the data has been anticipated through the data review process led by data management before database lock. This review of the data is anticipated to include a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

The protocol does not mention a preliminary analysis. A partial database lock and a preliminary analysis will be done on safety and immunogenicity data for V01 to V02 before the 6-month follow-up data is locked, but data from V01 through the 6-month follow-up will be included in the same CSR.

6 References List

1 Chatterjee A, O'Keefe C, Varman M, Klein NP, Luber S, Tomovici A, Noriega F. Comparative immunogenicity and safety of different multivalent component pertussis vaccine formulations and a 5-component acellular pertussis vaccine in infants and toddlers: a randomized, controlled, open-label, multicenter study. Vaccine. 2012 May 14;30(23):3360-8.

2 Newcombe R.G., Two-sided confidence intervals for the single proportion: comparison of seven methods, Stat. Med.1998; 17: 857-72.

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