

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-blinded, 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.

### Clinical Trial Protocol, Amendment 2

**Health Authority File Numbers:** BB-IND#: 16594

**WHO Universal Trial Number (UTN):** U1111-1161-3027

**Trial Code:** ADC01

**Development Phase:** Phase I/II

**Sponsor:** Sanofi Pasteur Inc.  
1 Discovery Drive, Swiftwater, PA 18370-0187, USA

**Investigational Product:** 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  $\geq$  10 years of age

**Manufacturer:** Same as Sponsor

**Coordinating Investigators:** [REDACTED]

**Sponsor's Responsible Medical Officer:** [REDACTED], Sanofi Pasteur Inc.

**Product Safety Officer:** [REDACTED], Sanofi Pasteur Inc.

**Clinical Trial Manager:** [REDACTED], Sanofi Pasteur Inc.

**Version and Date of the Protocol:** Version 3.0 dated 13 May 2016

This protocol version 3.0 is the second amendment to the initial trial protocol Version 1.0 dated 22 July 2015. It is preceded by Amendment 1.0 (protocol Version 2.0 dated 29 September 2015).

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## Synopsis

<b>Company:</b>	Sanofi Pasteur
<b>Investigational Product:</b>	SP0173 (Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Adsorbed [Tdap Vaccine])
<b>Active Substances:</b>	Tetanus toxoid (T), diphtheria toxoid (d), pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbriae types 2 and 3 (FIM).

<b>Title of the Trial:</b>	Safety and Immunogenicity of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Adsorbed (SP0173) in Healthy Adolescents, Adults, and Older Adults
<b>Development Phase:</b>	Phase I/II
<b>Coordinating Investigator:</b>	[REDACTED]
<b>Study Centers:</b>	This will be a multi-center study conducted at approximately 20 centers in the US. Investigators and sites are listed in the “List of Investigators, Trial Centers, and Sponsor’s Personnel Involved in the Trial Document.”
<b>Planned Trial Period:</b>	4Q 2015 to 1Q 2017
<b>Trial Design and Methodology:</b>	This will be a Phase I/II, randomized, modified double-blinded, 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. Age groups are defined as follows: <ul style="list-style-type: none"> <li>• Adolescents: age 10–18 years</li> <li>• Adults: age 19–64 years</li> <li>• Older Adults: age <math>\geq</math> 65 years</li> </ul> Subjects will be stratified by age group and will be randomized to the following 6 vaccination groups:



	review will be based on preliminary data that have not been subject to validation and database lock.
	<p>The following safety parameters will be assessed as part of the early safety review and the continuous safety analyses:</p> <ul style="list-style-type: none"> <li>• Immediate unsolicited AEs</li> <li>• Solicited injection site and systemic reactions</li> <li>• Unsolicited AEs</li> <li>• SAEs</li> <li>• MAAEs</li> </ul> <p>Enrollment will be paused during the ESDR, and the data will be examined for the following alert thresholds defined for this study:</p> <ul style="list-style-type: none"> <li>• Extensive limb swelling (ELS) among <math>\geq 3\%</math> recipients of any of the investigational formulations</li> <li>• Any life-threatening event or death considered related to vaccination by the Investigator among recipients of any of the investigational formulations</li> </ul> <p>If any of the above criteria are met during the per-group partially-blinded safety review, a decision will be made as to whether enrollment of the affected group in the study will be allowed to continue. Only in case of further concern, complete unblinding and further in-depth review of safety data will be conducted. Continuation will be determined pending final results of the early safety review. If the risk for certain formulation(s) has been determined as high, enrollment of the next age groups (adolescents and older adults) for the respective formulation will not proceed.</p> <p>The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined early interim safety analysis will continue unchanged.</p> <p>Apart from the ESDR and the ongoing safety review, the study may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the Institutional Ethics Committees (IEC)/Institutional Review Boards (IRB), or the governing regulatory authorities in the US where the study is taking place.</p> <p>If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the study is prematurely terminated for any reason, the Investigator will promptly inform the study subjects / subjects' parents/guardians and should assure appropriate therapy and follow-up.</p>
<b>Observational Objectives:</b>	<p><b><i>Safety / Reactogenicity</i></b></p> <ul style="list-style-type: none"> <li>• To describe the safety profile of each SP0173 investigational formulation.</li> </ul> <p><b><i>Immunogenicity</i></b></p> <ul style="list-style-type: none"> <li>• To describe the immunogenicity of each SP0173 investigational formulation.</li> </ul>

<p><b>Observational Endpoints:</b></p>	<p><b><i>Safety / Reactogenicity</i></b></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited (prelisted in the subject diary card [DC] and eCRF) injection site reactions and systemic reactions occurring through D7 after vaccination.</li> <li>• 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.</li> <li>• Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, seriousness criteria, relationship to vaccination, and outcome of SAEs from V01 to the 6-month follow-up for all groups after vaccination.</li> <li>• 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.</li> </ul> <p><b><i>Immunogenicity</i></b></p> <ul style="list-style-type: none"> <li>• Anti-pertussis (PT, FHA, PRN, and FIM) antibody concentrations pre- and post-vaccination measured by enzyme-linked immunosorbent assay (ELISA).</li> <li>• Anti-diphtheria antitoxin concentration pre- and post-vaccination assessed by toxin neutralization assay.</li> <li>• Anti-tetanus antitoxin concentration pre- and post-vaccination measured by ELISA.</li> </ul>																																													
<p><b>Planned Sample Size:</b></p>	<p>A total of 1350 subjects are planned to be enrolled and randomized to 1 of 6 study groups. Within each group subjects will be stratified by age in a 1:1:1 ratio as shown below.</p> <p><b>Table S2: Randomization by study group.</b></p> <table border="1"> <thead> <tr> <th rowspan="2">Study group</th> <th rowspan="2">Vaccine formulation</th> <th rowspan="2">Pertussis Adjuvant</th> <th colspan="3">Subjects, N</th> </tr> <tr> <th>10–18 years</th> <th>19–64 years</th> <th>≥ 65 years</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>SP0173-low</td> <td>██████</td> <td>75</td> <td>75</td> <td>75</td> </tr> <tr> <td>2</td> <td>SP0173-middle</td> <td>██████</td> <td>75</td> <td>75</td> <td>75</td> </tr> <tr> <td>3</td> <td>SP0173-middle</td> <td>██████</td> <td>75</td> <td>75</td> <td>75</td> </tr> <tr> <td>4</td> <td>SP0173-high</td> <td>██████</td> <td>75</td> <td>75</td> <td>75</td> </tr> <tr> <td>5</td> <td>Adacel<sup>®</sup> control</td> <td>██████</td> <td>75</td> <td>75</td> <td>75</td> </tr> <tr> <td>6</td> <td>BOOSTRIX<sup>®</sup> control</td> <td>██████</td> <td>75</td> <td>75</td> <td>75</td> </tr> </tbody> </table>	Study group	Vaccine formulation	Pertussis Adjuvant	Subjects, N			10–18 years	19–64 years	≥ 65 years	1	SP0173-low	██████	75	75	75	2	SP0173-middle	██████	75	75	75	3	SP0173-middle	██████	75	75	75	4	SP0173-high	██████	75	75	75	5	Adacel <sup>®</sup> control	██████	75	75	75	6	BOOSTRIX <sup>®</sup> control	██████	75	75	75
Study group	Vaccine formulation				Pertussis Adjuvant	Subjects, N																																								
		10–18 years	19–64 years	≥ 65 years																																										
1	SP0173-low	██████	75	75	75																																									
2	SP0173-middle	██████	75	75	75																																									
3	SP0173-middle	██████	75	75	75																																									
4	SP0173-high	██████	75	75	75																																									
5	Adacel <sup>®</sup> control	██████	75	75	75																																									
6	BOOSTRIX <sup>®</sup> control	██████	75	75	75																																									

Schedule of Study Procedures:	<p><b><u>Vaccination</u></b></p> <p>All subjects will be randomized to receive 1 dose of an SP0173 formulation, Adacel<sup>®</sup>, or BOOSTRIX<sup>®</sup>.</p>
	<p><b><u>Blood sampling</u></b></p> <p>All subjects will be asked to provide a pre-vaccination blood sample at V01 (D0) and a post-vaccination sample at V02 (30 days +14 days).</p> <p>A subset of subjects enrolled in all groups will provide an additional blood sample at baseline (pre-vaccination at V01) and a post-vaccination sample at V02 (30days +7 days) for exploratory testing of CMI parameters.</p> <p><b><u>Collection of safety data</u></b></p> <ul style="list-style-type: none"> <li>• All subjects will be observed for 30 minutes after vaccination and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the eCRF.</li> <li>• The subjects or subject's parent/guardian will record information about solicited reactions (injection site and systemic) in a DC from D0 to D7 post-vaccination. Unsolicited AEs and SAEs will be recorded in the DC between V01 and V02.</li> <li>• If the subject develops a Grade 3 solicited injection site (including ELS) or systemic AE the subject or subject's parent/guardian is required to contact the site immediately. The site staff must attempt for the subject to be seen at the study site within 24 hours to assess the extent of the reaction.</li> <li>• Staff will contact the subject or subject's parent/guardian by telephone on D8 (+3 days) to identify the occurrence of any SAE, Grade 3 solicited adverse reactions (including ELS) not yet reported and to remind him/her to complete the DC up to V02 and to bring it back at V02.</li> <li>• At V02, the completed DC will be reviewed with the subject or subject's parent/guardian and the DC will be collected. The subject or subject's parent /guardian will receive a memory aid (MA) to record information about unsolicited AEs from V02 until the 6-month (+14 days) telephone call.</li> <li>• Staff will contact the subject or subject's parent/guardian by telephone at 6 months (+14 days) post-vaccination to review the MA and identify the occurrence of any MAAEs* or SAEs that may not have been reported.</li> <li>• 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. MAAE that occur from V02 to the long-term safety phone call at approximately 6 months after vaccination will be recorded as unsolicited AEs in the MA. An MAAE that occurs within the study period and meets the definition of an SAE should be reported only as an SAE.</li> </ul> <p>*Note: 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</p>

	<p>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.</p> <ul style="list-style-type: none"> <li>The subject or subject's parent/guardian will be asked to notify the site immediately about potential SAEs at any time during the trial.</li> </ul>																																																						
<p><b>Duration of Participation in the Trial:</b></p>	<p>The duration of each subject's participation in the study will be approximately 6 months (180 days + 14 days).</p>																																																						
<p><b>Investigational Product:</b></p> <p><i>Form:</i></p>	<p><b>SP0173:</b> Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur Limited, Toronto, ON, Canada)</p> <p>Liquid</p> <p>Each 0.5 mL dose is formulated to contain (exact amounts of some ingredients will vary based on the dose specified for the particular randomized group [Table S3]).</p> <div style="background-color: black; width: 100%; height: 150px; margin-top: 10px;"></div>																																																						
<p><i>Route:</i></p> <p><i>Batch Number:</i></p>	<p><b>Table S3: SP0173 investigational formulations</b></p> <table border="1" data-bbox="651 1150 1430 1549"> <thead> <tr> <th></th> <th></th> <th colspan="2"></th> <th colspan="4"></th> <th></th> </tr> <tr> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> </tr> </thead> <tbody> <tr> <td>I</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>I</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>I</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>I</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p>Intramuscular (IM)</p> <p>CD0097AA, CD0100AA, CD0102AA, CD0103AA</p>																			I									I									I									I								
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<p><b>Control Product:</b></p> <p><i>Form:</i></p>	<p><b>Adacel<sup>®</sup>:</b> Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur Limited, Toronto, ON, Canada)</p> <p>Liquid</p>														
<p><i>Composition:</i></p> <p><i>Route:</i></p> <p><i>Batch Number:</i></p>	<p>Each 0.5 mL dose is formulated to contain:</p> <p><u>Active Ingredients:</u></p> <table border="0"> <tr> <td>Tetanus Toxoid (T)</td> <td>5 Lf</td> </tr> <tr> <td>Diphtheria Toxoid (d)</td> <td>2 Lf</td> </tr> <tr> <td colspan="2">Acellular Pertussis</td> </tr> <tr> <td>    Pertussis Toxoid (PT)</td> <td>2.5 µg</td> </tr> <tr> <td>    Filamentous Hemagglutinin (FHA)</td> <td>5 µg</td> </tr> <tr> <td>    Pertactin (PRN)</td> <td>3 µg</td> </tr> <tr> <td>    Fimbriae Types 2 and 3 (FIM)</td> <td>5 µg</td> </tr> </table> <p><u>Other Ingredients:</u></p> <p>1.5 mg AlPO<sub>4</sub> adjuvant (0.33 mg aluminum), 0.6% v/v 2-phenoxyethanol</p> <p>IM</p> <p>C4774AA</p>	Tetanus Toxoid (T)	5 Lf	Diphtheria Toxoid (d)	2 Lf	Acellular Pertussis		Pertussis Toxoid (PT)	2.5 µg	Filamentous Hemagglutinin (FHA)	5 µg	Pertactin (PRN)	3 µg	Fimbriae Types 2 and 3 (FIM)	5 µg
Tetanus Toxoid (T)	5 Lf														
Diphtheria Toxoid (d)	2 Lf														
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Pertactin (PRN)	3 µg														
Fimbriae Types 2 and 3 (FIM)	5 µg														
<p><b>Control Product:</b></p> <p><i>Form:</i></p> <p><i>Composition:</i></p> <p><i>Route:</i></p> <p><i>Batch Number:</i></p>	<p><b>BOOSTRIX<sup>®</sup>:</b> Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (GlaxoSmithKline Biologicals, Rixensart, Belgium, and Novartis Vaccines and Diagnostics GmbH Marburg, Germany)</p> <p>Liquid</p> <p>Each 0.5 mL dose contains:</p> <p><u>Active Ingredients:</u></p> <table border="0"> <tr> <td>Tetanus Toxoid (T)</td> <td>5 Lf</td> </tr> <tr> <td>Diphtheria Toxoid (d)</td> <td>2.5 Lf</td> </tr> <tr> <td colspan="2">Acellular Pertussis</td> </tr> <tr> <td>    Pertussis Toxoid (PT)</td> <td>8 µg</td> </tr> <tr> <td>    Filamentous Hemagglutinin (FHA)</td> <td>8 µg</td> </tr> <tr> <td>    Pertactin (PRN)</td> <td>2.5 µg</td> </tr> </table> <p><u>Other Ingredients:</u></p> <p>4.5 mg sodium chloride, ≤ 0.39 mg aluminum (AlOOH adjuvant), ≤ 100 µg residual formaldehyde, ≤ 100 µg polysorbate 80 (Tween 80)</p> <p>IM</p> <p>Commercial product to be supplied by the sites.</p>	Tetanus Toxoid (T)	5 Lf	Diphtheria Toxoid (d)	2.5 Lf	Acellular Pertussis		Pertussis Toxoid (PT)	8 µg	Filamentous Hemagglutinin (FHA)	8 µg	Pertactin (PRN)	2.5 µg		
Tetanus Toxoid (T)	5 Lf														
Diphtheria Toxoid (d)	2.5 Lf														
Acellular Pertussis															
Pertussis Toxoid (PT)	8 µg														
Filamentous Hemagglutinin (FHA)	8 µg														
Pertactin (PRN)	2.5 µg														
<p><b>Inclusion Criteria:</b></p>	<p>An individual must fulfill <i>all</i> of the following criteria in order to be eligible for study enrollment:</p> <ol style="list-style-type: none"> <li>1) Aged 10 to 18 years, 19 to 64 years, or ≥ 65 years on the day of inclusion.</li> <li>2) Informed consent form has been signed and dated by the subject, or assent form has been signed and dated by the subject and informed consent form has been signed and dated by the parent/guardian</li> <li>3) Subject or subject and parent/guardian able to attend all scheduled visits and to comply with all study procedures</li> </ol>														

<b>Exclusion Criteria:</b>	An individual fulfilling <i>any</i> of the following criteria is to be excluded from study enrollment:
	<ol style="list-style-type: none"> <li data-bbox="651 310 1430 489">1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination.)</li> <li data-bbox="651 499 1430 621">2) Participation at the time of study enrollment (or in the 4 weeks preceding the study vaccination) or planned participation during the present study period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure.</li> <li data-bbox="651 632 1430 785">3) Received any vaccine in the 4 weeks preceding the trial vaccination or planned receipt of any vaccine between V01 and V02. For influenza vaccine only, defer if received in the 14-day period prior to enrollment or scheduled to receive in the 14-day period after enrollment.</li> <li data-bbox="651 795 1430 926">4) Known or suspected receipt of a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine or Tdap-containing vaccine at any point in time, or receipt of a tetanus and diphtheria containing vaccine in the preceding 5 years.</li> <li data-bbox="651 936 1430 1003">5) Receipt of immune globulins, blood or blood-derived products in the past 3 months.</li> <li data-bbox="651 1014 1430 1167">6) Known or suspected congenital or acquired immunodeficiency, immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 6 months, or long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).</li> <li data-bbox="651 1178 1430 1245">7) History of diphtheria, tetanus, or pertussis infection (confirmed either serologically or microbiologically).</li> <li data-bbox="651 1255 1430 1356">8) Known or suspected systemic hypersensitivity to any of the vaccine components or history of life-threatening reaction to the study vaccine or a vaccine containing the same substances.</li> <li data-bbox="651 1367 1430 1434">9) Laboratory-confirmed/self-reported thrombocytopenia or bleeding disorder contraindicating IM vaccination.</li> <li data-bbox="651 1444 1430 1512">10) Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination</li> <li data-bbox="651 1522 1430 1675">11) History of encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures) not attributable to another identifiable cause within 7 days of administration of a previous dose of diphtheria and tetanus toxoids and pertussis (DTP), or diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine</li> <li data-bbox="651 1686 1430 1753">12) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.</li> <li data-bbox="651 1764 1430 1797">13) Current alcohol abuse or drug addiction.</li> <li data-bbox="651 1808 1430 1875">14) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion.</li> </ol>

	<p>15) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature <math>\geq 100.4^{\circ}\text{F}</math>). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.</p> <p>16) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study.</p>
<p><b>Statistical Methods:</b></p>	<p><b><u>Demographics</u></b></p> <p>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.</p> <p><b><u>Safety / Reactogenicity</u></b></p> <p>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.</p> <p>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.</p> <p><b><u>Immunogenicity</u></b></p> <p>For <i>pertussis</i>, immunogenicity of SP0173 investigational formulations will be assessed by comparison of post-vaccination GMCs to the following:</p> <ul style="list-style-type: none"> <li>• In adolescents and adults: booster response rates and antibody GMCs after a single Adacel<sup>®</sup> dose</li> <li>• In older adults: booster response rates to pre-determined criteria and antibody GMCs after 3 doses of DTaP (Daptacel<sup>®</sup>) 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)</li> </ul>

	<p>For sera obtained after vaccination, in addition to unadjusted GMCs, GMCs will be computed using analysis of covariance to adjust for baseline disparities.</p> <p>For <i>diphtheria and tetanus</i>, 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<sup>®</sup> dose.</p> <p>Booster response rates partially adjust for individual and population differences in pre-vaccination antibody concentrations.</p> <p>The criteria for demonstrating a pertussis booster response are as follows:</p> <ul style="list-style-type: none"> <li>• If the pre-booster vaccination concentration is <math>&lt; 4xLLOQ</math>, then the post-booster vaccination concentration is <math>\geq 4x</math> the pre-booster concentration*</li> <li>• If the pre-booster vaccination concentration is <math>\geq 4xLLOQ</math>, then the post-primary vaccination concentration is <math>\geq 2x</math> the pre-booster concentration</li> </ul> <p>* Pre-booster vaccination concentrations <math>&lt; LLOQ</math> will be converted to LLOQ for purposes of calculating this booster response.</p> <p>For diphtheria and tetanus the criteria for demonstrating a booster response are as follows:</p> <ul style="list-style-type: none"> <li>• Subjects whose pre-vaccination antibody concentrations are <math>&lt; 0.1</math> IU/mL will demonstrate the booster response if they have a post-vaccination level <math>\geq 0.4</math> IU/mL</li> <li>• Subjects whose pre-vaccination antibody concentrations are <math>\geq 0.1</math> IU/mL but <math>&lt; 2.0</math> IU/mL will demonstrate the booster response if they have a 4-fold rise (i.e., post-/pre-vaccination <math>\geq 4</math>)</li> <li>• Subjects whose pre-vaccination antibody concentrations are <math>\geq 2.0</math> IU/mL, will demonstrate the booster response if they have a 2-fold response (i.e., post-/pre-vaccination <math>\geq 2</math>)</li> </ul> <p>Seroprotection rates will be presented separately for diphtheria and tetanus as:</p> <ul style="list-style-type: none"> <li>• Proportion of subjects pre- and post-vaccination with anti-diphtheria antitoxin concentration <math>\geq 0.01</math>, <math>\geq 0.10</math>, and <math>\geq 1.0</math> IU/mL</li> <li>• Proportion of subjects pre- and post-vaccination with anti-tetanus antitoxin concentration <math>\geq 0.01</math>, <math>\geq 0.10</math>, and <math>\geq 1.0</math> IU/mL</li> </ul> <p>As an observational control, pre-and post-vaccination GMCs and booster response rates (for pertussis, diphtheria, and tetanus), as well as seroprotection rates (for diphtheria and tetanus only) will also be calculated for adolescent, adult, and older adult subjects who receive BOOSTRIX<sup>®</sup>.</p>
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	<p><u>Calculation of Sample Size</u></p> <p>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 are anticipated.</p>
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## 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)
<b>Study timelines (days)</b>	D0	D8	D30	D180
<b>Time windows (days)</b>		[+3 Days]	[+ 14 Days]*	[+14 days]
Informed consent form/Assent form (if applicable) <sup>†</sup>	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) <sup>‡</sup>	X			
Verbal medical and vaccination history	X			
Physical examination <sup>§</sup>	X			
Collection of Concomitant Therapy**	X			
Measure circumference of both arms <sup>††</sup>	X			
Randomization/allocation of subject number	X			
Blood sampling (BL), approximately 10–20 mL <sup>‡‡</sup>	BL1		BL2	
<b>Vaccination</b>	X			
Immediate surveillance (30 min)	X			
Diary card provided	X			
Telephone contact <sup>§§</sup>		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 <sup>***</sup>			X	
Recording of MAAEs <sup>†††</sup>			Visit 02 to TC2	
Recording of SAEs	To be reported at any time during the study			
Follow-up telephone call <sup>‡‡‡</sup>				X
Completion of 6-month follow-up				X

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\*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.

\*\*As specified in [Section 6.7](#).

††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.

## List of Abbreviations

ap	acellular pertussis (lower content)
aP	acellular pertussis (higher content)
AE	adverse event
AR	adverse reaction
CDM	Clinical Data Management
CLC	Clinical Logistics Coordinator
CMI	cell mediated immunity
CRA	Clinical Research Associate
eCRF	electronic case report form
CTA	clinical trial agreement
CTL	Clinical Team Leader
d	reduced diphtheria toxoid
D	day
DC	diary card
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
ELS	extensive limb swelling
ESDR	early safety data review
FAS	full analysis set
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
FVFS	first visit, first subject
FVLS	first visit, last subject
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPV	Global PharmacoVigilance
IATA	International Air Transport Association
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug (application)
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LCLS	last contact, last subject

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LLT	[MedDRA] lowest level term
LLOQ	lower limit of quantification
MA	memory aid
MAAE	medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
OG	Operating Guidelines
PPAS	per-protocol analysis set
PRN	pertactin
PSO	Product Safety Officer
PT	pertussis toxoid
RMO	Responsible Medical Officer
SAE	serious adverse event
SafAS	safety analysis set
SMT	safety management team
T	tetanus toxoid
TMF	trial master file
ULOQ	upper limit of quantification
US	United States
V	Visit
WHO	World Health Organization

# 1 Introduction

## 1.1 Background

### Tetanus

Tetanus is an acute and often-fatal infection caused by an extremely potent neurotoxin produced by *Clostridium tetani*, which is most commonly found in soil (1). The disease is characterized by severe, painful muscle contractions, accompanied by hypersensitivity, hyperreflexia, and increased autonomic stimulation of the affected body part(s). Complications associated with tetanus include laryngospasms, spinal and long bone fractures, and hypertension (2). Tetanus occurs sporadically worldwide, but it is uncommon in developed countries, mainly because of immunization and hygienic precautions taken in the management of wound and surgical procedures.

### Diphtheria

Diphtheria is an acute infection caused by *Corynebacterium diphtheriae*. The main site of infection is the upper respiratory tract, characterized by a patch of grayish pseudomembrane surrounded by inflammation. Complications associated with diphtheria include airway obstruction, myocarditis, and paralysis. The case-fatality rate runs as high as 30–95%, particularly in the elderly, despite modern medical care (3).

### Pertussis

Pertussis (whooping cough) is a highly contagious infectious disease of the respiratory tract caused by *Bordetella pertussis*. The illness is characterized by severe coughing spasms, which may or may not be associated with the classic inspiratory whoop. Although pertussis is most severe and complications are most frequent in children less than one year of age, pertussis can affect persons of any age (4). Antimicrobial therapy is effective in eradicating the organism from the respiratory tract but does not alter the progression of the disease unless given in the early stage when pertussis is rarely suspected; therefore, control of the disease has been based on vaccine prophylaxis (5).

## 1.2 Background of the Investigational Product

The proposed updated Tdap vaccine, under evaluation in Study ADC01, will include the same antigenic components as Adacel<sup>®</sup>. The investigational formulations differ from Adacel<sup>®</sup> 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 selection of Tdap formulations to be evaluated in Study ADC01 was based on safety and immunogenicity data obtained with varying antigen concentrations in clinical trials conducted in different age groups, as well as data from a range of in vitro formulation and process development studies and animal immunogenicity evaluations.

## 1.3 Potential Benefits and Risks

### 1.3.1 Potential Benefits to Subjects

Subjects in all groups will be vaccinated with either one of the four investigational Tdap formulations or a licensed Tdap vaccine (Adacel<sup>®</sup> or BOOSTRIX<sup>®</sup>) and will likely gain benefit against infectious disease through boosting of their immunity to diphtheria, tetanus and pertussis.

### 1.3.2 Potential Risks to Subjects

Based on safety data from previous trials with similar products, potential risks of the study vaccines are limited to the usual injection site reactions expected following any injectable vaccine such as pain, redness and swelling. Fever may also occur but is generally mild in intensity. Extensive Limb Swelling (ELS) has been reported in a small proportion of individuals following vaccination with acellular pertussis vaccines and may be more common following booster doses. All these reactions resolve spontaneously, usually within a few days after vaccination.

As with any vaccine, investigational Tdap vaccine formulations may not protect 100% of individuals against the diseases they are designed to prevent.

The risks associated with blood drawing include injection site pain, bruising, and (rarely) fainting or infection.

Tdap is contraindicated in persons with known systemic hypersensitivity to any of their components or a history of life-threatening reaction to the vaccine or to a vaccine containing the same substances. Because of uncertainty as to which vaccine component may be responsible, no further vaccination with the diphtheria, tetanus, or pertussis components found in Tdap should be carried out.

Please see the Investigator Brochure for complete descriptions of the potential risks associated with Tdap vaccines.

## 1.4 Rationale for the Trial

The overall goal of this Phase I/II Study is to select a formulation for further clinical development of SP0173 (Tetanus Toxoid [T], Reduced Diphtheria Toxoid [d] and Acellular Pertussis Vaccine Adsorbed [ap]) as a combination pertussis vaccine formulation (Tdap) to boost immunity towards the targeted diseases in individuals  $\geq 10$  years of age.

In Study ADC01, SP0173 antibody GMCs will be evaluated in 1 of 2 ways, depending on subject age. In subjects  $< 65$  years of age, SP0173 antibody GMCs for T, d, and pertussis antigens will be compared with Adacel<sup>®</sup>. In subjects  $\geq 65$  years of age SP0173 antibody GMCs for T and d will be compared with Adacel<sup>®</sup>, 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) (6) studies. The immunogenicity objectives of Study ADC01 are observational and therefore the study is not powered to detect statistically significant differences in antibody responses between candidate formulations or to assess non-inferiority to historical controls.

Collectively, safety and immunogenicity data will be essential determinants of the suitability of a candidate vaccine formulation for advancement to Phase III clinical development.

## 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.

The endpoints for the observational objectives are presented in [Section 9.3.1.2](#) and [Section 9.3.2.1](#).

## 3 Investigators and Trial Organization

This study will be conducted in approximately 20 centers in the US. Details of the study centers and the Investigators at each center are provided in the “List of Investigators and Centers Involved in the Trial” document.

The safety of the investigational product will be continuously monitored by the Sponsor and will include 3 types of surveillance:

- *Ongoing safety surveillance* of SAE.
- *Periodic safety surveillance* (during enrollment and safety data collection for each of the 2 sets of age cohorts: adults followed by adolescents/older adults) [REDACTED]
- *Early Safety data review (ESDR)*, during which enrollment in the study (between age cohorts) will be paused. [REDACTED]

Immunogenicity testing will all be performed at the Sanofi Pasteur Global Clinical Immunogenicity (GCI) laboratories in Swiftwater, PA, USA.

The Sponsor's Responsible Medical Officer (the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [REDACTED], [REDACTED], Clinical Team Leader (CTL) or such delegate as may be identified in her absence.

## 4 Independent Ethics Committee/Institutional Review Board

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form (ICF), subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and/or receive favorable opinion from, the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

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

The Investigator will submit written summaries of the status of the trial to the IEC/IRB annually, or more frequently if requested. All SAEs occurring during the trial that are related to vaccination will be reported by the Investigator to the IEC/IRB, according to the IEC/IRB policy.

## 5 Investigational Plan

### 5.1 Description of the Overall Trial Design and Plan

#### 5.1.1 Trial Design

This will be 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 US.

Subjects' age groups are defined as follows:

- Adolescents: age 10–18 years
- Adults: age 19–64 years
- Older Adults: age  $\geq$  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<sup>®</sup>, or BOOSTRIX<sup>®</sup> (Table 5.1).

**Table 5.1: Study groups and vaccine formulations**

Study Group	Vaccine Formulation	Age Group		Vaccine Components				Other
		Adolescent	Adult	PT	PRN	FIM	FHA	
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

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 V01 (D0) to V02 (D30-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 follow-up (D180) as MAAEs. An MAAE that occurs within the study period but meets the definition of an SAE should be reported as an SAE.

All subjects will be asked to provide a blood sample for immunogenicity assessment at baseline (pre-vaccination at V01) and at V02. A subset of subjects (36 adolescents, 60 adults and 60 older adults) enrolled in all groups will provide an additional pre- and post-vaccination blood sample for exploratory testing of parameters of cell-mediated immunity (CMI). The results of that testing will be described in a separate report.

**5.1.2 Justification of the Trial Design**

The proposed Phase I/II study, ADC01, will be the first trial in humans to evaluate the different formulations of SP0173 (low-, middle- and high-dose) when adjuvanted to either [REDACTED] or [REDACTED] and administered to adolescent, adults and older adults, i.e. the key target age groups where administration of a tetanus, diphtheria and pertussis vaccine is recommended by the Advisory Committee on Immunization Practices in the US. The dose of pertussis antigens to be explored in all age groups varies for the PT, PRN and FIM components and is the same in all formulations for the FHA component.

The selection of investigational Tdap formulations to be evaluated in ADC01 was based on safety and immunogenicity data obtained with varying antigen concentrations in clinical trials conducted in different age groups, as well as data from a range of *in vitro* formulation and process

development studies and animal immunogenicity evaluations. The immunogenicity of each formulation is enhanced by the presence of an [REDACTED].

As a safety precaution, Study ADC01 will employ a step-down approach for enrollment: adult subjects (age 19–64 years) will be enrolled and vaccinated, and an internal review of safety data collected through D30 after injection will be conducted; an acceptable review of safety data and an acceptable safety profile based on prospectively defined criteria will be required before concurrent enrollment of adolescent (age 10–18 years) and older adult subjects (age  $\geq$  65 years).

### 5.1.3 Trial Plan

Eligible subjects will be identified and enrolled at each research center. Initially, enrollment will be restricted to the subjects in the adult age group (19–64 years of age). Enrollment of adolescent and older adult subjects is planned subsequent to a satisfactory review of safety data from V01 through V02 post-vaccination for the adult age group.

Each subject and/or subjects' parent/guardian must sign and date the ICF (and assent form for subjects under the age of legal majority [according to state regulation]) before any procedure or treatment associated with the study is performed.

Subjects will receive one injection of either SP0173 vaccine, Adacel<sup>®</sup>, or BOOSTRIX<sup>®</sup> on D0. Each subject will be asked to provide a blood sample (10–20 mL/bleed<sup>a</sup>) to be collected before vaccine injection at V01 (D0) and at V02 (30 days [ $\pm$  14 days<sup>b</sup>] after injection).

All subjects and/or subjects' parent/guardian will be asked to record solicited injection site reactions and solicited systemic reactions that occur for 7 days after the injection and unsolicited AEs that occur from V01(D0) through V02 (D30). SAEs will be collected throughout the study period from D0 through D180 after vaccination. MAAEs will be collected throughout the study from V01 through V02 (as part of the collection of unsolicited AEs) and from V02 through D180 (as MAAEs).

### 5.1.4 Visit Procedures

#### V01 (D0): Inclusion, Randomization, Applicable Blood Sample, and Vaccination

- 1) Give the subject or subject's parent/guardian information about the study.
- 2) Obtain informed consent and assent (for subjects under the legal age of majority [according to state regulations]) and answer any questions to ensure that the subjects and/or subject's parent/guardian have been informed of all aspects of the trial that are relevant to their decision to participate. Document the informed consent process in the subject's record.

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<sup>a</sup> Most subjects will provide approximately 10 mL of blood at each blood draw. Subjects enrolled in the CMI subset will provide an additional 10 mL of blood pre- and post-vaccination.

<sup>b</sup> For subjects in the CMI subset, the V02 window will be between Day 30 and Day 37.

- 3) Date and sign the ICF (and assent form for subjects under the legal age of majority [according to state regulations]) after it has been signed and dated by the subject or subject's parent/guardian. Retain the original and give a signed copy to the subject or subject's parent/guardian.
- 4) Check inclusion and exclusion criteria for eligibility.
- 5) Collect demographic information.
- 6) For women of childbearing potential<sup>a</sup>, obtain a urine pregnancy test.
- 7) Obtain verbal medical and vaccination history about the subject (including relevant prior and concomitant therapy).
- 8) Perform and document a limited physical examination per standard site-specific immunization practices. If a routine physical examination was performed at the same clinical site no more than 30 days before V01, verify and record any changes in the subject's health status and update with a signature, noting review by someone delegated to perform a physical examination. Measure and record temperature. If the temperature is  $\geq 100.4^{\circ}\text{F}$ , postpone vaccinations until the condition is resolved.
- 9) Call the IVRS/IWRS for assignment of the subject number, randomization to study group, and allocation of the product to be administered (should be performed by the unblinded administrator).
- 10) Obtain pre-vaccination blood sample (see [Section 7.1](#) for detailed instructions regarding the handling of blood samples).
- 11) Instruct the subject or subject's parent/guardian how to perform and record the arm circumference measurements. The subject or subject's parent/guardian will be requested, under the supervision of the study staff, to perform the baseline measurement of both arms. Record the circumference of both arms in the source document and transcribe that of the vaccinated arm in the subject's DC.
- 12) Administer the study or control vaccine intramuscularly in the deltoid region of the arm.
- 13) Keep the subject under observation for 30 minutes, and record any adverse reaction in the source documents and electronic case report form (eCRF).
- 14) Provide the DC to the subject or subject's parent/guardian and ask them to record in it solicited injection site and systemic reactions for D0 to D7. Ask them to use the DC to record any unsolicited AEs (from V01 to V02) and concomitant medications. MAAEs that occur from V01 to V02 will be recorded as unsolicited AEs on the DC as part of the unsolicited AEs collected for this post-vaccination period. Provide appropriate training including ruler, measuring tapes, digital thermometer, and instructions for use.

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<sup>a</sup> To be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception, or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination.

- 15) Instruct the subject or subject's parent/guardian to expect a telephone contact on D8 post-vaccination to identify the occurrence of any SAE, Grade 3 solicited adverse reactions (including ELS) not yet reported and to remind him/her to complete the DC up to V02 and bring it back at V02. The date of the appointment for V02 will be confirmed.
- 16) If the subject develops a Grade 3 solicited injection site or systemic AE (see [Table 9.1](#) and [Table 9.2](#)), develop significant change in arm circumference (increased  $\geq 50$  mm from pre-vaccination measurement at baseline), or ELS which occur during the 7-day period after vaccination, the subject or subject's parent/guardian is required to contact the site immediately. The site staff must attempt for the subject to be seen at the study site within 24 hours to assess the extent of the reaction. In cases of Grade 3 injection site swelling or ELS, the subject (or parent/guardian) is to be instructed to take measurements of the vaccinated arm circumference, and record in the DC, until the swelling is resolved (See Operating Guidelines [OG] for details).
- 17) Set up an appointment for V02 (D30–D44) and instruct the subject or subject's parent/guardian to bring the DC to the visit to discuss the information entered with the study personnel.

*Note: For subjects in the CMI subset, the V02 window will be between D30 and D37*

- 18) Remind the subject or subject's parent/guardian to notify the site in case of an SAE.
- 19) Complete the relevant case report form (eCRF) pages for this visit.

#### Telephone Call 1 (D8 + 3 Days)

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

- 1) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE, Grade 3 solicited adverse reaction (including ELS) has occurred, follow the instructions in [Section 10](#) for reporting it.
- 2) Remind the subject or subject's parent/guardian to do the following:
  - Continue to complete the DC, and bring it to V02.
  - Notify the site in case of an SAE.
- 3) Confirm V02 appointment.

#### V02 (window 30–44<sup>a</sup> days after V01): Collection of Safety Information and Blood Sample

- 1) Collect the DC. Review the pages of the DC with the subject or subject's parent/guardian, including any AEs, concomitant medications, or therapy and medical visits that occurred since vaccination.
- 2) Obtain the second blood sample (see [Section 7.1](#) for detailed instructions regarding the handling of blood samples).

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<sup>a</sup> For subjects in the CMI subset, the V02 window will be between D30 and D37

- 3) Give the subject or subject's parent/guardian a memory aid (MA) and provide instructions for the MA completion. Inform them to expect the 6-month telephone follow-up.

#### Telephone Call 2 (D180 +14 days)

- 1) Review the MA with the subject or subject's parent/guardian.
- 2) Record relevant information concerning the subject's health status on the telephone contact form. If an SAE or MAAE occurred, follow the instructions in [Section 10](#) for reporting it.
- 3) Complete the relevant eCRF forms for this call, as well as the termination record in the eCRF.

#### ***SAEs and AEs That Are Related to Vaccination or That Led to Discontinuation:***

At any time during the study, a subject who experiences an SAE or an AE must be followed if *either* of the following is true:

- The SAE or AE is considered by the Investigator to be related to vaccination, and is not resolved by the end of the subject's participation in the trial
- The subject has been discontinued from the trial because of the SAE or AE

Any such subject must be followed until the condition resolves, becomes stable, or becomes chronic.

#### **5.1.5 Planned Trial Calendar**

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

Planned trial period - FVFS (first visit, first subject) to LVLS (last visit, last subject):

Adult Subjects: October 2015–July 2016

Adolescent Subjects: April 2016–April 2017

Older Adult Subjects: May 2016–March 2017

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

Adult Subjects: October 2015–December 2015

Adolescent Subjects: April 2016–October 2016

Older Adult Subjects: May 2016–September 2016

Planned primary vaccination period: Please see dates for planned trial period

Planned end of trial<sup>a</sup>: April 2017

Planned date of final clinical study report: November 2017

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<sup>a</sup> End of trial is defined as the date of the last contact with a subject i.e. 6-month follow-up telephone call

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

[REDACTED]

Study continuation will be determined pending final results of the ESDR and any potential investigation(s). If the risk for certain SP0173 formulation(s) has been determined as high, enrollment of the next age groups (adolescents and older adults) for the respective formulation will not proceed.

In addition to the ESDR, the usual and ongoing process of monitoring safety signals will continue unchanged (See [Section 3](#)).

Apart from the ESDR and the ongoing safety review, the study may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the IEC/IRB, or the governing regulatory authorities in the US where the study is taking place.

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the study is prematurely terminated for any reason, the Investigator will promptly inform the study subjects/subjects' parents/guardians and should assure appropriate therapy and follow-up.

## 5.2 Enrollment and Retention of Trial Population

### 5.2.1 Recruitment Procedures

Subjects may be recruited from the general population. The site will ensure that any advertisements used to recruit subjects (informational brochures, letters, pamphlets, posters, and other advertisements) are submitted to Sanofi Pasteur prior to submission to the IRB for approval.

### 5.2.2 Informed Consent Procedures

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

For this study, in addition to the ICF that is signed by the subject's parent/guardian, subjects that have not reached the legal age of majority (according to state regulations) will be asked to review and sign a separate informed assent form.

In accordance with GCP, prior to signing and dating the consent and assent form, the subject (or the adolescent subject and their parent/guardian) must be informed by appropriate study personnel about all aspects of the trial that are relevant to making the decision to participate, and must have sufficient time and opportunity to ask any questions.

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

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

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

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

In designated study sites, a convenience sample of 36 adolescents (10–18 years of age), 60 adults (19–64 years of age), and 60 older adults ( $\geq 65$  years) will be invited to provide an additional blood sample for CMI testing. An addendum to the ICF will be prepared to request voluntary provision of an additional blood sample (approximately 10 mL) for the test. Prior to signing and dating the addendum, the subject (or the adolescent subject and their parent/guardian) must be provided by appropriate study personnel with the relevant information for making the decision, and must have sufficient time and opportunity to ask any questions. A photocopy of the signed CMI addendum will be made and given to the subject.

### 5.2.3 Screening Criteria

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

### 5.2.4 Inclusion Criteria

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

- 1) Aged 10 to 18 years<sup>a</sup>, 19 to 64 years<sup>b</sup>, or  $\geq 65$  years<sup>c</sup> on the day of inclusion.
- 2) Informed consent form has been signed and dated by the subject, or assent form has been signed and dated by the subject and informed consent form has been signed and dated by the parent/guardian.
- 3) Subject or subject and parent/guardian able to attend all scheduled visits and to comply with all study procedures.

### 5.2.5 Exclusion Criteria

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

- 1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination<sup>d</sup>).
- 2) Participation at the time of study enrollment (or in the 4 weeks preceding the study vaccination) or planned participation during the present study period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure.
- 3) Received any vaccine in the 4 weeks preceding the trial vaccination or planned receipt of any vaccine between V01 and V02. For influenza vaccine only, defer if received in the 14-day period prior to enrollment or scheduled to receive in the 14-day period after enrollment.
- 4) Known or suspected receipt of a tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine, or Tdap-containing vaccine at any point in time, or receipt of a tetanus and diphtheria-containing vaccine in the preceding 5 years.
- 5) Receipt of immune globulins, blood or blood-derived products in the past 3 months.

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<sup>a</sup> “10 to 18 years” means from the day of the 10th birthday to the day before the 19th birthday

<sup>b</sup> “19 to 64 years” means from the day of the 19th birthday to the day before the 65th birthday

<sup>c</sup> “ $\geq 65$  years” means from the day of the 65th birthday or older

<sup>d</sup> For pre-menarche females, the young female subjects will declare by themselves if they have not yet started menstruation. If a young female subject reaches menarche during the study, then she is to be considered as a woman of childbearing potential from that time forward.

- 6) Known or suspected congenital or acquired immunodeficiency, immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 6 months, or long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).
- 7) History of diphtheria, tetanus, or pertussis infection (confirmed either serologically or microbiologically).
- 8) Known or suspected systemic hypersensitivity to any of the vaccine components or history of life-threatening reaction to the study vaccine or a vaccine containing the same substances<sup>a</sup>.
- 9) Laboratory-confirmed / self-reported thrombocytopenia or bleeding disorder contraindicating IM vaccination.
- 10) Bleeding disorder or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination.
- 11) History of encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures) not attributable to another identifiable cause within 7 days of administration of a previous dose of diphtheria and tetanus toxoids and pertussis (DTP), or diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.
- 12) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.
- 13) Current alcohol abuse or drug addiction.
- 14) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion.
- 15) Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature  $\geq 100.4^{\circ}\text{F}$ ). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided.
- 16) Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study.

If the subject has a primary physician who is not the Investigator, the site—with the subject's consent—must make a reasonable and timely attempt to contact the primary physician to inform him/her of the subject's participation in the study. In addition, the site should ask the primary physician to verify exclusion criteria relating to medical history and previous therapies (such as receipt of previous vaccines, blood products, or immunosuppressive therapies). If contact with the subject's primary physician is unsuccessful, the subject may still be enrolled in the study so long as the Investigator considers the subject eligible to participate (i.e., the subject meets all inclusion criteria and does not meet any exclusion criteria).

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<sup>a</sup> The components of SP0173 and comparator products are listed in [Section 6.1](#) and in the Investigator's Brochure.

### 5.2.6 Medical History

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

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

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

The reporting of signs and symptoms is strongly discouraged.

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

### 5.2.7 Contraindications for Subsequent Vaccinations

Not applicable since only one dose of vaccine will be administered in this trial.

### 5.2.8 Conditions for Withdrawal

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

- In any situation where, in the opinion of the Investigator, continuation in the study would not be in the best interest of the subject due to safety concerns (withdrawal) without the subject's permission
- At the request of the subject (drop out)

The following will result in automatic withdrawal or exclusion of a subject from the study:

- Significant non-compliance with the protocol, based on the Investigator's judgment

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

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

Withdrawn subjects will not be replaced.

### 5.2.9 Lost to Follow-up Procedures

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

### 5.2.10 Classification of Subjects Who Discontinue the Trial

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

- **Serious adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an SAE, as defined in [Section 9.3.1.1](#).
- **Other adverse event:** To be used when a subject drops out of or is withdrawn from the study by the Investigator because of the occurrence of an AE other than an SAE, as defined in [Section 9.3.1.1](#).
- **Non-compliance with protocol:** To be used when the Investigator withdraws a subject from the study because of failure to follow the protocol including when it is retrospectively discovered that a subject did not fulfill the eligibility criteria. The Investigator will provide a comment as to the specific cause of non-compliance.
- **Lost to follow-up:** To be used when the Investigator withdraws a subject from the study because of failure to establish contact, as outlined in [Section 5.2.9](#). The Investigator will provide documentation that contact was attempted (i.e., return of unsigned certified letter receipt).
- **Voluntary withdrawal not due to an adverse event:** To be used when a subject drops out of the study for any reason other than those listed above.

### 5.2.11 Follow-up of Discontinuations

The site should complete all scheduled safety follow-ups and contact any subject who has prematurely terminated the trial because of an SAE, other type of AE, non-compliance with the protocol, or loss of eligibility, including definite contraindications.

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

### 5.2.12 Follow-up and Reporting of Pregnancies

Pregnancy is an exclusion criterion for enrollment in this study, but a subject could potentially become pregnant during her participation. In case of pregnancy and if study vaccine has been administered, the subject will not be discontinued from the trial and will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

All pregnancy cases should be reported if they occurred during the study. To report the pregnancy case, the Investigator must fill out a Pregnancy Reporting Form in the electronic data capture (EDC) system and send it to the Sponsor within 1 month of identifying a pregnancy case.

Study staff must then maintain contact with the subject to obtain information about the outcome—i.e., details about the delivery and the newborn, or about pregnancy termination—and must update the electronic Pregnancy Reporting Form. This information should be provided to the Sponsor within 1 month of delivery.

Pregnancy itself is not considered an AE, but any complications during pregnancy are to be considered as AEs, and in some cases could be considered SAEs. Spontaneous abortions, fetal death, stillbirth, and congenital anomalies reported in the baby are always considered as SAEs, and the information should be provided to the Global Pharmacovigilance (GPV) Department regardless of when the SAE occurs (e.g., even after the end of the trial).

### 5.3 Safety Emergency Call

If, as per the Investigator's judgment, a subject experiences a medical emergency, the Investigator may contact the Sponsor's Responsible Medical Officer (RMO) for advice on trial related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the OG.

This process does not replace the need to report an SAE. The investigator is still required to follow the protocol defined process for reporting SAEs to GPV (Please refer to [Section 10](#)).

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

### 5.4 Modification of the Trial and Protocol

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

An administrative amendment to a protocol is one that modifies some administrative or logistical aspect of the trial but does not affect its design or objectives or have an impact on the subjects' safety. Regulatory authorities need only be notified about administrative changes. Administrative changes do not require IRB approval; however, the IRB must be notified whenever one is made. The Investigator is responsible for ensuring that changes to an approved trial, during the period for which IEC/IRB approval has already been given, are not initiated without IEC/IRB review and approval, except to eliminate apparent immediate hazards to subjects.



### 6.1.1.2 Preparation and Administration

SP0173 vaccine is a liquid preparation; as such, no diluent is required. After shaking, the vaccine is a white to off-white homogenous cloudy suspension. SP0173 vaccine should be administered as a single 0.5 mL injection by the intramuscular route, preferably in the deltoid region, using a needle not less than 1 inch (25 mm) in length. Before injection, the skin at the injection site should be cleansed and prepared with a suitable germicide.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see [Section 6.3.1](#)), and extraneous particulate matter and/or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. A replacement dose is to be used, and the event is to be reported to the Sponsor. Subjects must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRF. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic or other immediate allergic reaction.

### 6.1.1.3 Dose Selection and Timing

SP0173 vaccine will be administered to all Group 1–4 subjects as a single 0.5 mL dose at V01.

## 6.1.2 Identity of Control Product 1

**Adacel<sup>®</sup>**: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap), Sanofi Pasteur Limited, Toronto, ON, Canada

**Form:** Liquid Solution

**Dose:** 0.5 mL

**Route:** IM

**Batch number:** C4774AA

### 6.1.2.1 Composition

Each 0.5 mL dose of vaccine contains the following components:

#### Active Ingredients

Tetanus toxoid (T)	5 Lf
Diphtheria toxoid (d)	2 Lf
Acellular Pertussis	
Pertussis toxoid (PT)	2.5 µg
Filamentous Hemagglutinin (FHA)	5 µg
Pertactin (PRN)	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg

Other Ingredients

1.5 mg AlPO<sub>4</sub> adjuvant (0.33 mg aluminum), 0.6% v/v 2-phenoxyethanol

**6.1.2.2 Preparation and Administration**

The procedures for preparing and administering this control product are the same as those described for the trial product in [Section 6.1.1.2 \(7\)](#).

**6.1.2.3 Dose Selection and Timing**

Adacel<sup>®</sup> will be administered to all Group 5 subjects as a single 0.5 mL dose at V01.

**6.1.3 Identity of Control Product 2**

**BOOSTRIX<sup>®</sup>**: Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap), GlaxoSmithKline Biologicals, Rixensart, Belgium and Novartis Vaccines and Diagnostics GmbH (Marburg, Germany)

**Form:** Liquid solution

**Dose:** 0.5 mL

**Route:** IM

**Batch number:** Commercial product to be supplied by the sites.

**6.1.3.1 Composition**

Each 0.5 mL dose of vaccine contains the following components:

Active Ingredients:

Tetanus toxoid (T)	5 Lf
Diphtheria toxoid (d)	2.5 Lf
Acellular Pertussis	
Pertussis toxoid (PT)	8 µg
Filamentous Hemagglutinin (FHA)	8 µg
Pertactin (PRN)	2.5 µg

Other Ingredients:

4.5 mg sodium chloride

≤ 0.39 mg aluminum (aluminum oxyhydroxide adjuvant)

≤ 100 µg residual formaldehyde

≤ 100 µg polysorbate 80 (Tween 80)

### 6.1.3.2 Preparation and Administration

BOOSTRIX<sup>®</sup> will be prepared and administered according to manufacturer's package insert (8).

### 6.1.3.3 Dose Selection and Timing

BOOSTRIX<sup>®</sup> will be administered to all Group 6 subjects as a single 0.5 mL dose at V01.

## 6.2 Identity of Other Products

Not applicable.

## 6.3 Product Logistics

### 6.3.1 Labeling and Packaging

*Primary packaging: Vial*

SP0173 will be supplied in single-dose vials with a clinical label.

Adacel<sup>®</sup> will be supplied in single-dose vials with the manufacturer's commercial labeling retained on the vial.

*Outer packaging: Cardboard box*

SP0173 vials will be in individual cartons with a clinical label.

Adacel<sup>®</sup> will be in individual cartons.

BOOSTRIX<sup>®</sup> will be purchased by the sites for use in this study.

### 6.3.2 Product Shipment, Storage, and Accountability

#### 6.3.2.1 Product Shipment

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

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

### 6.3.2.2 Product Storage

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

At the site, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The vaccines must not be frozen. The temperature must be monitored and documented (see the OG) for the entire time that the vaccine is at the trial site. In case of accidental freezing or disruption of the cold chain, vaccines must not be administered and must be quarantined, and the Investigator or authorized designee should contact the Sanofi Pasteur representative for further instructions.

### 6.3.2.3 Product Accountability

The person in charge of product management at the site will maintain records of product delivery to the trial site, product inventory at the site, the unique dosing number (IVRS kit number) given to each subject, and the disposal of or return to the Sponsor of unused doses.

The necessary information on the product labels is to be entered into the source document and the eCRF.

The Sponsor's monitoring staff will verify the trial site's product accountability records against the record of administered doses in the CRFs and the communication from the IVRS/IWRS (if applicable).

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

### 6.3.3 Replacement Doses

If a replacement dose is required (e.g., because the vial broke or particulate matter was observed in the vial), the site personnel must either contact the IVRS/IWRS to receive the new dose allocation, or follow the instructions given in the OG.

### 6.3.4 Disposal of Unused Products

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

### 6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Investigators will be informed of what needs to be done.

## 6.4 Blinding and Code-breaking Procedures

As the presentation of the investigational and control vaccines differs, an observer-blinded procedure will be followed in the study, so that neither the Investigator (who is in charge of the

safety assessment), nor the subject's or the subject's parent/guardian, nor the Sponsor will know which vaccine has been administered. The product preparation and administration, and the assessment of safety will be performed by 2 different individuals in 2 different rooms.

The Investigator or delegate will include the subjects and will evaluate the safety during the 30 minute period after each vaccination, but will not be aware of which vaccine (investigational or control) has been administered (i.e., the Investigator will be a blinded observer for safety).

The blinded staff members, including the Investigator responsible for safety assessment, will not attend the vaccination session. However, they will remain available in case of emergency (e.g., anaphylactic shock).

The vaccinator (unblinded vaccine administrator) will prepare and administer the vaccine in a separate room, according to the IVRS/IWRS subject treatment allocation.

Product accountability forms will be kept in a secure place to which only the unblinded vaccine administrator in charge of vaccination has access. The Sponsor's monitoring staff in charge of product management will be unblinded to the randomization.

Emergency unblinding will be managed by the IVRS/IWRS, using the dose number.

The code may be broken by the Investigator only in the event of an SAE and if identification of the vaccine received could influence the treatment of the SAE. Code-breaking should be limited, as far as possible, to the subject experiencing the SAE. If time allows, every effort should be made to discuss with the Sponsor RMO before unblinding the subject.

The blind can be broken by the Investigator or a sub-investigator (medical doctor only<sup>a</sup>), by calling the IVRS/IWRS system as explained in the code-breaking procedures described in the OG. Once the emergency has been addressed by the site, the Investigator must notify the Sanofi Pasteur RMO if a subject's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents.

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

- by GPV department for reporting to Health authorities in the case of an SAE as described in ICH E2A. In this case, the code will be broken only for the subject in question. The information resulting from code-breaking (i.e., the subject's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

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

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<sup>a</sup> according to local regulations.

## 6.5 Randomization and Allocation Procedures

The Sponsor or designee will supply a centralized, age- and site-stratified, computer-generated randomization code. The computer-generated randomization code will assign subjects to 1 of 6 groups.

Each subject who meets the eligibility criteria and signs an informed consent form will be randomly assigned to 1 of 6 groups via an IVRS/IWRS Site. Unblinded site staff will call the IVRS/IWRS, enter identification and security information, and confirm a minimal amount of data in response to IVRS/IWRS prompts. The IVRS/IWRS will then state the subject number and the group subset, and have the caller confirm this. Subject numbers will be recorded on the eCRFs. The full detailed procedures for randomization are described in the OG.

Subject numbers will be 8 digits long, with a 3-digit center identifier and a 5-digit subject identifier. For example, Subject 001-00001 is the first subject enrolled in center number 1.

Subject numbers should not be reassigned for any reason.

## 6.6 Treatment Compliance

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

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

## 6.7 Concomitant Medications and Other Therapies

At the time of enrollment, ongoing medications including other therapies e.g., vaccines, blood products, should be recorded in the source document as well as new medications prescribed for new medical conditions/AEs during trial participation.

Documentation in the CRF of concomitant medication will be limited to specific categories of medication of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the eCRF from the day of vaccination to the end of the solicited and unsolicited follow-up period (e.g., 30 day safety follow-up) as they may impact the response to the vaccination and impact the consistency of the information collected on concomitant medications at any vaccination.

The “reportable” medications are distributed according to two categories. These are:

- Category 1 antipyretics, analgesics, non-steroidal anti-inflammatory drugs, corticosteroids, and other immune modulators.

*Note: inhaled and topical steroids should not be captured.*

- Category 2: Other reportable medications as specified in the protocol (i.e., medications related to exclusion criteria [please refer to [Section 5.2.5](#)] and contraindications, if not captured as Category 1 medications) and other medications as noted here. All non-study vaccines, immune globulins, and blood or blood-derived products are included in this category.

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

- Trade name
- Given as treatment or as prophylaxis
- Medication category
- Start and stop dates

(Note: prophylaxis is defined as medication taken to prevent any AEs that may occur following the administration of the study vaccine during the solicited follow-up period.)

Dosage and administration route will not be recorded. Homeopathic medication will not be recorded. Topical treatment will not be recorded.

The fact that a medication was given in response to an AE will be captured in the “Action Taken” column of the AE only. No details will be recorded in the concomitant medication module of the CRF unless the medication received belongs to one of the prelisted categories. Medications will not be coded.

## 7 Management of Samples

Blood samples for the assessment of antibody responses and cellular immunity analysis will be collected at V01 and at V02. See the [Table of Study Procedures](#) and [Section 5.1.3](#) for details of the sampling schedule.

### 7.1 Sample Collection

#### 7.1.1 Serum Samples

At V01 and V02, approximately 10 mL of blood (or approximately 20 mL of blood for subjects in the CMI subset) will be collected in tubes provided by or recommended by the Sponsor.

Immediately prior to the blood draw, the staff member performing the procedure will verify the subject’s identity; will write the assigned subject's number on the pre-printed label that contains that subject’s number and the sampling stage; and will attach the label to the tube. Blood is to be taken from the limb opposite to the one that will be used for vaccination.

#### 7.1.2 Blood Samples for Cellular Immunity Assessment

Blood samples for cellular immunity assessment will be collected at V01 and V02. Samples (approximately 10 mL) will be collected in heparinized plastic tubes and will then be processed for cell isolation and freezing. Labeling will be done according to the procedure described in the OG for CMI testing.

## 7.2 Sample Preparation

### 7.2.1 Serum Samples

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

Following the blood draw, the tubes are to be left undisturbed, positioned vertically and not shaken, for a minimum of 1 hour and a maximum of 24 hours in order to allow the blood to clot. Samples can be stored at room temperature for up to 2 hours; beyond 2 hours, they must be refrigerated at a temperature of +2°C to +8°C after the period of clotting at room temperature and must be centrifuged within a maximum of 24 hours.

The samples are then centrifuged, and the serum is transferred to the appropriate number of aliquoting tubes. These tubes are pre-labeled with adhesive labels that identify the study code, the subject's number and the sampling stage or visit number.

The subject's number and the date of sampling, the number of aliquots obtained, the date and time of preparation, and the subject's consent for future use of his / her samples are to be specified on a sample identification list and recorded in the source document. Space is provided on this list for comments on the quality of samples.

### 7.2.2 Blood for Cellular Immunity Assessment

Blood for cellular immunity analysis will be collected in BD Vacutainer<sup>®</sup> Plus plastic plasma tube, light green BD Hemogard<sup>™</sup> closure. Samples should not be centrifuged and should be kept at room temperature. Labeling will be done according to the procedure described in the OG for CMI testing. Details on sample handling will be provided in the OG.

## 7.3 Sample Storage and Shipment

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

Shipments to the laboratories will be made only after appropriate monitoring, and following notification of the CLC. Sera will be shipped frozen, using dry ice to maintain them in a frozen state, in the packaging container provided by the carrier. Again, temperatures will be monitored. Shipments must be compliant with the International Air Transport Association (IATA) 602 regulations.

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

The whole-blood sample for cellular immunity analysis will be stored at room temperature, and will be transported to the designated CMI laboratory within the next 8 hours after collecting the sample. The address is provided in the OG.

## 7.4 Future Use of Stored Serum/Blood Samples for Research

Any unused part of the serum / blood samples will be securely stored at the Sanofi Pasteur GCI laboratory for a minimum of 5 years after licensure in the relevant market area. Blood samples collected for CMI testing will be stored up to 5 years after completion of the study.

The subjects or subject's parent/guardian will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. (Anonymity of samples will be ensured.) The aim of any possible future research is unknown today, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve laboratory methods. Genetic tests will never be performed on these samples without individual informed consent.

## 8 Clinical Supplies

Sanofi Pasteur will supply the trial sites with protocols, ICFs, Assent forms, Addenda for CMIs, CRFs, SAE reporting forms, diary cards, memory aids, and other trial documents, as well as with the following trial materials: all study vaccines and injection materials, blood collection tubes, cryotubes, cryotube storage boxes, cryotube labels, temperature recorders, shipping containers, rulers, and digital thermometers.

The means for performing EDC will be defined by Sanofi Pasteur. If a computer is provided by Sanofi Pasteur, it will be retrieved at the end of the trial.

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

In the event that additional supplies are required, study staff must contact Sanofi Pasteur, indicating the quantity required. Contact information is provided in the OG. They must allow approximately 1 week for an order to be filled and to have the supplies sent to their site.

## 9 Endpoints and Assessment Methods

### 9.1 Primary Endpoints and Assessment Methods

#### 9.1.1 Safety

There are no primary objectives for safety.

### 9.1.2 Immunogenicity

There are no primary objectives for immunogenicity.

### 9.1.3 Efficacy

No clinical efficacy data will be obtained in the trial.

## 9.2 Secondary Endpoints and Assessment Methods

There are no secondary objectives in this study.

### 9.2.1 Safety

There are no secondary objectives for safety.

### 9.2.2 Immunogenicity

There are no secondary objectives for immunogenicity.

### 9.2.3 Efficacy

No clinical efficacy data will be obtained in the trial.

## 9.3 Observational Endpoints and Assessment Methods

### 9.3.1 Safety

#### 9.3.1.1 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<sup>a</sup>
- Requires inpatient hospitalization or prolongation of existing hospitalization<sup>b</sup>
- Results in persistent or significant disability / incapacity<sup>c</sup>
- Is a congenital anomaly / birth defect
- Is an important medical event<sup>d</sup>

***Adverse Reaction:***

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

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<sup>a</sup> 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.

<sup>b</sup> 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.

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

<sup>d</sup> 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 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.

(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<sup>a</sup> is an AR at and around the injection site. Injection site reactions are commonly inflammatory 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.

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<sup>a</sup> All injection site AEs are considered to be related to vaccination and are therefore all *injection site reactions*.

### ***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.

#### **9.3.1.2 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.

#### **9.3.1.3 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.

##### **9.3.1.3.1 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, according to the procedures described in [Section 10](#).

### 9.3.1.3.2 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 9.1](#) and [Table 9.2](#) present, respectively, the injection site reactions and systemic reactions that are prelisted in the DCs and CRF, together with the intensity scales.

**Table 9.1: 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: $\geq 25$ to $\leq 50$ mm Grade 2: $\geq 51$ to $\leq 100$ mm Grade 3: $> 100$ mm	Grade 1: $\geq 25$ to $\leq 50$ mm Grade 2: $\geq 51$ to $\leq 100$ mm Grade 3: $> 100$ mm	Grade 1: $> 0$ to $< 25$ mm increase over pre-vaccination measurement Grade 2: $\geq 25$ to $< 50$ mm increase over pre-vaccination measurement Grade 3: $\geq 50$ 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. See procedure in [Section 5.1.4](#).

† 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 9.2: Solicited systemic reactions: terminology, definitions, and intensity scales**

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia
<b>Diary card term</b>	Temperature*	Headache*	Feeling unwell*	Muscle aches and pains*
<b>Definition</b>	Elevation of temperature to $\geq 100.4^{\circ}\text{F}$	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.
<b>Intensity scale**</b>	Grade 1: $\geq 100.4^{\circ}\text{F}$ to $\leq 101.1^{\circ}\text{F}$ Grade 2: $\geq 101.2^{\circ}\text{F}$ to $\leq 102.0^{\circ}\text{F}$ Grade 3: $\geq 102.1^{\circ}\text{F}$	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. See procedure in [Section 5.1.4](#).

\*\*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 ( $\geq 50$  mm over pre-vaccination measurement at baseline) or ELS<sup>a</sup> (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 OG for details).

**9.3.1.3.3 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<sup>b</sup>
- 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 9.1](#) and [Table 9.2](#)).

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<sup>a</sup> 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

<sup>b</sup> 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)

#### **9.3.1.3.4 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 9.3.1.3.7](#).

See [Section 10](#) for further details on SAE reporting.

#### **9.3.1.3.5 Adverse Events of Special Interest**

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

#### **9.3.1.3.6 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.

### 9.3.1.3.7 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<sup>a</sup>:

- 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.

## 9.3.2 Immunogenicity

### 9.3.2.1 Immunogenicity Endpoints

- Anti-pertussis (PT, FHA, PRN, and FIM) antibody concentrations pre- and post-vaccination measured by enzyme-linked immunosorbent 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

### 9.3.2.2 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

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<sup>a</sup> ICH Guidelines, Clinical Safety Data Management E2A

amount of specific antibody bound to the wells. The results are read on a spectrophotometer (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<sub>2</sub>), 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 ≤ 7.0) contained in the medium. In the absence of neutralizing antibodies, the challenge toxin reduces cellular metabolism and CO<sub>2</sub> production, therefore the pH does not decrease and a color change is not detected. The LLOQ is 0.005 IU/mL.

### **9.3.3 Efficacy**

No clinical efficacy data will be obtained in the trial.

## **10 Reporting of Serious Adverse Events**

In order to comply with current regulations on SAE reporting to health authorities, the Investigator must document all SAEs regardless of causal relationship, and notify the Sponsor and the Clinical Research Associate (CRA) within the notification timelines stated in the following sections. The Investigator will give access and provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational products. It is the responsibility of the Investigator to request all necessary documentation (e.g., medical records, discharge summary, autopsy) in order to provide comprehensive safety information. All relevant information must then be transcribed into the eSAE Form.

## 10.1 Initial Reporting by the Investigator

SAEs occurring during a subject's participation in the trial or experiment must be reported within 24 hours to the Sponsor's GPV Department and to the CRA. Every SAE must be reported, even if the Investigator considers that it is not related to the vaccine. The SAE form must be signed by a licensed physician (MD or DO) for whom the task is listed on the Study Task Delegation and Signature List after each update to the Form.

The Investigator must complete the "eSAE Form" in the EDC application. After validation, an e-mail alert will automatically be sent to the GPV mailbox, the CRA and the Clinical Team Leader (CTL). This message will include the country, the study code, the subject number, whether the report is initial or a follow-up, the diagnosis and/or symptoms, the seriousness criteria, the relationship, if related, and the outcome, if fatal.

If the EDC system is unavailable, the site must notify the Sponsor using the paper version of the SAE Reporting Form, as follows:

The Investigator must complete the SAE Reporting Form, check off the "Initial Reporting Form" box, and send it to the Sponsor by one of the following means:

- By fax, to the following number: [REDACTED]
- In PDF format to the following e-mail address, using a method of transmission that includes password protection: [REDACTED]
- By express mail, to the following address:

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

When the system becomes available, the Investigator must transcribe the information from the paper version of the eSAE Form into the EDC system.

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

## 10.2 Follow-up Reporting by the Investigator

The eSAE Form completed initially must be updated within 24 hours after the Investigator has become aware of any new relevant information concerning the SAE (e.g., outcome, precise description of medical history, results of the investigation). After validation, an e-mail alert will be sent automatically to the GPV Department and to the CRA. All relevant information must be included directly in the eSAE form. Copies of documents (e.g., medical records, discharge summary, autopsy) may be requested by the GPV Department.

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

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

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

### 10.4 Assessment of Causality

The causal relationship between the SAE and the product will first be evaluated by the Investigator, using the following definitions:

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

**1 - Related:** There is a “reasonable possibility” that the SAE was caused by the vaccination, meaning that there is evidence or arguments to suggest a causal relationship.

*(ICH Guidelines, Clinical Safety Data Management E2A)*

Following this, the Sponsor’s Product Safety Officer (PSO) will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The decision to modify or discontinue the trial may be made after mutual agreement between the Sponsor and the Investigators.

### 10.5 Reporting SAEs to Health Authorities and IECs / IRBs

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

The Sponsor’s Responsible Medical Officer, will notify the Investigators in writing of the occurrence of any reportable SAEs. The Investigators / Sponsor will be responsible for informing the IECs or IRBs that reviewed the trial protocol.

## 11 Data Collection and Management

### 11.1 Data Collection and CRF Completion

Individual safety DCs, specifically designed for this trial by the Sponsor and provided to the study sites, will be given to study subjects for the recording of daily safety information as described in [Section 9.3.1.3.2](#). These DCs will include prelisted terms and intensity scales (see [Table 9.1](#) and [Table 9.2](#)) as well as areas for free text to capture additional safety information or other relevant details. Memory aids will be provided to collect safety information between V02 and the long-

term safety call. Subjects or subjects' parents or guardians will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct subjects or subjects' parents or guardians on how to correctly use these tools.

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

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

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

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

## 11.2 Data Management

### *Management of Clinical Data*

Data generated during the trial will be managed following two different processes:

- Clinical data, defined as all data reported in the eCRF, and laboratory data will be handled by the Sponsor's Clinical Data Management (CDM) platform or authorized representative.
- Data pertaining to SAEs, which are reported by the Investigator on the eSAE Forms or SAE Reporting Forms, will be handled by the Sponsor's GPV Department.

During the trial, clinical data reported in the eCRFs will be integrated into the clinical database under the responsibility of the Sanofi Pasteur CDM platform. Data monitoring at the sites and quality control in the form of computerized logic and/or consistency checks will be systematically applied in order to detect errors or omissions. In addition, data reviews may be performed several times by the Sponsor's staff in the course of the trial. Any questions pertaining to the reported

clinical data will be submitted to the investigator for resolution using the EDC system. Each step of this process will be monitored through the implementation of individual passwords to maintain appropriate database access and to ensure database integrity.

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

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

### ***SAE Data Management***

During the trial, data pertaining to SAEs reported on eSAE Forms will be integrated into the Sponsor's centralized GPV database.

Upon receipt of an eSAE Form, the data will be entered into the GPV database after a duplicate check. Each SAE case will be assigned a case identification number. All cases will be reviewed and assessed by the PSO. Each case is reviewed, locked, and approved in the GPV database before being reported to the relevant authorities as necessary. Follow-up information concerning a locked and approved case will be entered into the GPV database, and a new version of the case will be created.

The information pertaining to SAEs in the GPV database will be reconciled with that in the clinical database.

## **11.3 Data Review**

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

# **12 Statistical Methods and Determination of Sample Size**

## **12.1 Statistical Methods**

### **12.1.1 Statistical Methods for Demographics and Background Characteristics**

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.

## 12.1.2 Statistical Methods for Observational Objectives

### Safety/Reactogenicity

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 (Days 0 to 3, Days 4 to 7, and Days 0 to 7 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 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 and from V02 through the end of the 6-month follow-up period.

### Immunogenicity

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<sup>®</sup> dose.

Booster Response Rates partially adjusted for individual and population differences in pre-vaccination antibody concentrations.

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  $\geq 4x$  the pre-booster concentration\*
- If the pre-booster vaccination concentration is  $\geq 4xLLOQ$ , then the post-primary vaccination concentration is  $\geq 2x$  the pre-booster concentration.

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

- In older adults: booster response rates to pre-determined criteria and antibody GMCs after 3 doses of DTaP (Daptacel<sup>®</sup>) 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.

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<sup>®</sup> dose.

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

Seroprotection rates will be presented separately for diphtheria and tetanus as:

- Proportion of subjects pre- and post-vaccination with anti-diphtheria antitoxin concentration  $\geq 0.01$ ,  $\geq 0.10$ , and  $\geq 1.0$  IU/mL
- Proportion of subjects pre- and post-vaccination with anti-tetanus antitoxin concentration  $\geq 0.01$ ,  $\geq 0.10$ , and  $\geq 1.0$  IU/mL

As an observational control, pre-and post-vaccination GMCs and booster response rates (for pertussis, diphtheria, and tetanus), as well as seroprotection rates (for diphtheria and tetanus only) will also be calculated for adolescent, adult, and older adult subjects who receive BOOSTRIX<sup>®</sup>.

## 12.2 Analysis Sets

### 12.2.1 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.

### 12.2.2 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).

### 12.2.3 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
- 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 serology sample did not produce a valid test result

#### **12.2.4 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. Subjects will be analyzed according to the vaccine they actually received.

### **12.3 Handling of Missing Data and Outliers**

#### **12.3.1 Safety**

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

#### **12.3.2 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.

### **12.4 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.

## 12.5 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.

## 13 Ethical and Legal Issues and Investigator/Sponsor Responsibilities

### 13.1 Ethical Conduct of the Trial/Good Clinical Practice

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

### 13.2 Source Data and Source Documents

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

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

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

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

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

### 13.3 Confidentiality of Data and Access to Subject Records

Prior to initiation of the trial, the Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur.

Sanofi Pasteur personnel (or designates), the IECs/IRBs, and regulatory agencies, including the Food and Drug Administration, require direct access to all study records, and will treat these documents in a confidential manner.

### 13.4 Monitoring, Auditing, and Archiving

#### 13.4.1 Monitoring

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

The following instruction manuals will be provided: the eCRF Completion Guidelines for entering data into the eCRF, and the OG for detailed trial procedures such as the product management and sample-handling procedures.

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

- Evaluate the quality of the trial progress (adherence to protocol and any study-specific guidelines, quality of data collection and document completion, signature of consent forms, occurrence of SAEs, sample and product management, cold-chain monitoring, archiving)
- Source-verify completed eCRFs and any corresponding answered queries
- Determine the number of complete or ongoing issues identified at monitoring visits (e.g., protocol deviations, SAEs). Any identified problems will be discussed with the Investigator, and corrective or preventive actions will be determined, as appropriate
- After all protocol procedures have been completed and the data have been entered into the CRF, the Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock

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

- The center has all the documents necessary for archiving

- All samples have been shipped to the appropriate laboratories
- All unused materials and products have been either destroyed or returned to the Sponsor

#### **13.4.2 Audits and Inspections**

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

#### **13.4.3 Archiving**

The Investigator must keep all trial documents after the completion or discontinuation of the trial, whatever the nature of the investigational center (private practice, hospital, or institution), for as long as required by applicable laws and regulations. In the absence of any applicable laws or regulations, trial documents will be kept at a minimum for the duration indicated on the Clinical Trial Agreement (CTA). In no event, should study personnel destroy or permit the destruction of any trial documents upon less than 90 days advance written notification to the Sponsor. In addition, trial documents should continue to be stored, at Sponsor's sole expense, in the event that the Sponsor requests in writing that such storage continues for a period of time that exceeds that required by any applicable law or regulation or the CTA. The Investigator will inform Sanofi Pasteur of any address change or if they will no longer be able to house the trial documents.

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

#### **13.5 Financial Contract and Insurance Coverage**

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

#### **13.6 Stipends for Participation**

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

#### **13.7 Publication Policy**

Data derived from this trial are the exclusive property of Sanofi Pasteur. Any publication or presentation related to the trial must be submitted to Sanofi Pasteur for review before submission

of the manuscript. After publication of the results of the trial, any participating center may publish or otherwise use its own data provided that any publication of data from the trial gives recognition to the trial group. In addition, Sanofi Pasteur shall be offered an association with all such publications, it being understood that Sanofi Pasteur is entitled to refuse the association.

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

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

## 14 References List

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- 4 Pertussis. Division of Immunization and Respiratory Diseases, Health Canada, 2014. Available at: <http://www.phac-aspc.gc.ca/im/vpd-mev/pertussis-eng.php>. Accessed 30 August 2015.
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- 6 Chatterjee A, O'Keefe C, Varman M, Klein NP, Lubber 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.
- 7 Adacel [package insert]. Sanofi Pasteur Limited (Toronto, Canada).
- 8 BOOSTRIX [package insert]. GlaxoSmithKline Biologicals (Rixensart, Belgium) and Novartis Vaccines and Diagnostics GmbH (Marburg, Germany).



## 15 Signature Pages

<b>Document Number</b> CLI_1436268	<b>Version Number</b> 3.0
<b>Project Code</b> SP0173	
<b>Document Name</b> Protocol body	

	<b>Approver Name</b>	<b>Date (Universal Time)</b>	<b>Reason for Signature</b>
<b>Approval</b>	[REDACTED] Director of Clinical Development (sanofi pasteur)	19 May 2016 10:30:27	I am approving this document
<b>Approval</b>	[REDACTED] Director of Clinical Development (sanofi pasteur)	19 May 2016 10:34:39	I am approving this document