NCT02915302

Safety and Immunogenicity of Fluzone® Quadrivalent Vaccine Administered to Healthy Children 6 to < 36 Months of Age

Phase IV, randomized, observer-blinded, 2-arm, multi-center trial to evaluate the safety and immunogenicity of 2 different dose levels of Fluzone® Quadrivalent vaccine in healthy children 6 to < 36 months of age

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	GRC88
Development Phase:	Phase IV
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product(s):	Fluzone® Quadrivalent, Influenza Vaccine (2016–2017 formulation)
Form / Route:	Liquid/Intramuscular
Indication For This Study:	To evaluate the safety and immunogenicity of 2 different dose levels of Fluzone Quadrivalent vaccine (2016–2017 formulation) in children 6 to < 36 months of age
Version and Date of the SAP core body part:	Version 2.0, 20 July 2017

Table of Contents

List of Tables

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AR	Adverse Reaction
BL	Blood Sample
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDM	Clinical Data Management
CI	Confidence Interval
CSR	Clinical Study Report
DC	Diary Card
dil	Dilution
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GCI	Global Clinical Immunology
GM	Geometric Mean
GMT	Geometric Mean Titer
HAU	Hemagglutination Unit
HAI	Hemagglutination Inhibition
IRT	Interactive Response Technology
LLOQ	Lower Limit of Quantification
MD	Missing Data
MedDRA	Medical Dictionary for Regulatory Activities
NM	Non-Measurable
PPAS	Per-Protocol Analysis Set
PT	Preferred Term
RBC	Red Blood Cell
RCDC	Reverse Cumulative Distribution Curve
SAE	Serious Adverse Event
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
TLF	Table(s), Listing(s), and Figure(s)

ULOQ	Upper Limit of Quantification
WHO	World Health Organization

1 Introduction

This is a trial evaluating the safety and immunogenicity in children of 2 different dose levels of the 2016–2017 formulation of quadrivalent inactivated influenza vaccine (Fluzone® Quadrivalent, Influenza Vaccine). To assess whether a higher dose of Fluzone Quadrivalent vaccine might induce a more robust antibody response (and potentially offer improved protection) among children 6 through 35 months of age, this trial will compare the safety and immunogenicity of a full dose (15 µg HA per strain in 0.5-mL volume) of the vaccine versus a half dose (7.5 µg HA per strain in 0.25-mL volume).

Because children 6 through 23 months of age are at substantially increased risk for influenza-related hospitalizations, and children 24 through 59 months of age are at increased risk for influenza-related clinic and emergency department visits, the Advisory Committee on Immunization Practices (ACIP) has recommended annual vaccination of all eligible children in these age groups. In recent years, ACIP has further expanded the targeted age groups, and now recommends that all eligible people 6 months of age and older receive annual influenza vaccination (1) (2). The ACIP continues to emphasize the importance of vaccinating persons ≥ 6 months of age who have high-risk medical conditions (1)

If a child 6 months through 8 years of age is receiving influenza vaccine for the first time, based on ACIP recommendations, 2 doses of influenza vaccine should be administered during the current season. This recommendation is based on studies demonstrating that vaccine effectiveness is lower among children who have never received influenza vaccine previously or who received only 1 dose in their first year of vaccination than it is among children who received 2 doses in their first year of being vaccinated. Children 6 months through 8 years of age who are adequately primed, based on influenza vaccination history, should receive 1 dose during the current season as per ACIP recommendations (1) (2).

Vaccine efficacy and effectiveness studies have generally demonstrated that inactivated influenza vaccines reduce influenza disease in children, but in some studies the effectiveness in children 6 through 35 months of age is lower than that in children 3 years of age and older. The practice of administering a half-dose of inactivated influenza vaccine to young children originates from experience with whole-virus vaccine, which was reactogenic and frequently caused fever in young children. Split-virus and subvirion influenza vaccines are less reactogenic and data from the studies cited above support the safety of the full-dose in this population. Further, data from recent studies suggest that in children 6 through 35 months of age, full-dose influenza vaccine induces generally higher antibody responses compared to those induced by half-dose vaccine, without causing materially higher rates of systemic or injection site reactions. In most studies, differences in antibody responses between the full- and half-dose groups were greatest in the youngest age cohorts (i.e., 6- through 11-month-old or 6- through 23-month-old children).

[redacted]

Based on the foregoing, there is a strong rationale to allow use of the 0.5-mL dose for young children. Consequently, the purpose of the study described herein is to describe the safety and immunogenicity of the 0.5-mL dose (15 µg HA per strain) of Fluzone Quadrivalent vaccine in children 6 through 35 months of age, with the intent to modify the vaccine's Prescribing Information (Dosage and Administration) to show the 0.5-mL dose of Fluzone Quadrivalent vaccine as indicated for all ages 6 months and older, including children 6 months through 8 years of age (who might receive 1 or 2 doses as recommended by the ACIP).

2 Trial Objectives

2.1 Primary Objective

To compare the rate of any fever (temperature ≥ 100.4°F [38.0°C]) following the 0.5-mL dose of Fluzone Quadrivalent vaccine to that following the 0.25-mL dose of Fluzone Quadrivalent vaccine during the 7 days after either vaccination (Dose 1 and Dose 2 combined) in subjects 6 to < 36 months of age.

The endpoint for the primary objective is presented in Section 4.1.

2.2 Secondary Objective

To compare antibody responses induced by the 0.5-mL dose of Fluzone Quadrivalent vaccine to those induced by the 0.25-mL dose of Fluzone Quadrivalent vaccine as assessed by geometric mean titer (GMT) ratios and seroconversion rate differences after the final vaccination in subjects 6 to < 36 months of age.

The endpoints for the secondary objectives are presented in Section 4.2.

2.3 Observational Objectives

2.3.1 Safety

To describe the safety of 2 different dose levels of the 2016–2017 formulation of Fluzone Quadrivalent vaccine in subjects 6 to < 36 months of age.

The endpoints for the observational safety objective are presented in Section 4.3.1.2.

2.3.2 Immunogenicity

To describe the immunogenicity of 2 different dose levels of the 2016–2017 formulation of Fluzone Quadrivalent vaccine in subjects 6 to < 36 months of age.

The endpoints for the observational immunogenicity objective are presented in Section 4.3.2.1.

2.3.3 Serum Collection

[redacted]

There are no endpoints for the serum collection objective.

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This will be a Phase IV, randomized, observer-blinded, 2-arm, multi-center trial to evaluate the safety and immunogenicity of 2 different dose levels of Fluzone Quadrivalent vaccine in approximately 2190 healthy children 6 to < 36 months of age.

3.2 Trial Plan

Using a pre-programmed interactive response technology (IRT) system, subjects will be randomly assigned in a 1:1 ratio to either 1 of the following groups:

- Group 1: 0.25 mL of Fluzone Quadrivalent vaccine (approximately 1095 subjects)
- Group 2: 0.5 mL of Fluzone Quadrivalent vaccine (approximately 1095 subjects)

Enrollment will be stratified by age at each site so that approximately 50% of subjects at each site will be 6 to < 24 months of age and approximately 50% of subjects at each site will be 24 to < 36 months of age. If necessary to achieve 50% overall enrollment of subjects 6 to < 24 months of age, individual sites may be permitted to deviate from this ratio.

All subjects will receive 1 intramuscular dose of Fluzone Quadrivalent vaccine (0.25 mL [Group 1] or 0.5 mL [Group 2]) during Visit 1. For subjects for whom 2 doses of influenza vaccine are recommended per ACIP guidance, a second dose of Fluzone Quadrivalent vaccine (same 0.25-mL or 0.5-mL dose as administered at Visit 1) will be administered during Visit 2 (28 [window, 28–35] days after Visit 1).

Blood specimens will be obtained from a planned subset of approximately 1600 subjects randomly selected by an IRT system (half in Group 1 and half in Group 2) prior to the first vaccination and 28 (window, 28–35) days following the final vaccination (Visit 2 for subjects receiving 1 dose; Visit 3 for subjects receiving 2 doses) and assayed for immunogenicity.

Solicited AE information will be collected for 7 days after each vaccination. Unsolicited AE information and serious adverse event (SAE) information will be collected from Visit 1 to Visit 2 for subjects receiving 1 dose or from Visit 1 to Visit 3 for subjects receiving 2 doses.

Note: Any SAE that occurs after a subject has completed the study but that is likely to be related to the product is to also be reported to the Sponsor.

Table 3.1: Study Procedures - Trial Flow Chart for Subjects 6 to < 36 Months of Age: 2 or 3 Visits, 1 or 2 Vaccinations, 2 Groups

	All Subjects		Subjects Receiving 1 Dose of Influenza Vaccine	Subjects Receiving 2 Doses of Influenza Vaccine		
Visit Number	**Visit 1**	**Telephone Contact**	**Visit 2**	**Visit 2**	**Telephone Contact**	**Visit 3**
Trial Timelines	**Day 0**	**Visit 1 + 8 days**	**Visit 1 + 28 days**	**Visit 1 + 28 days**	**Visit 2 + 8 days**	**Visit 2 + 28 days**
Time Windows	--	**+ 8 to 10 days**	**+ 28 to 35 days**	**+ 28 to 35 days**	**+ 8 to 10 days**	**+ 28 to 35 days**
Informed consent	X					
Inclusion & Exclusion Criteria	X					
Demographic data	X					
Medical history	X					
Influenza vaccination history	X					
History-directed physical examination	X			X		
Temperature	X			X		
Allocation of subject number/Randomization	X					
Blood sample (BL) [a]	BL1		BL2			BL2
Vaccination[b,c]	X			X		
Immediate surveillance (20 minutes)	X			X		
Diary card (DC) provided	DC1			DC2		
Telephone contact[d]		X			X	

	All Subjects		Subjects Receiving 1 Dose of Influenza Vaccine	Subjects Receiving 2 Doses of Influenza Vaccine		
Diary card reviewed and collected			DC1	DC1		DC2
Interim history			X	X		X
Termination record[e]			X			X
Serious adverse events	To be reported throughout the study period					

[a] A blood sample, approximately 5 mL, will be collected from subjects randomly assigned to the immunogenicity subset at Visit 1, prior to vaccination, and at either Visit 2 (for subjects receiving 1 influenza vaccine dose) or at Visit 3 (for subjects receiving 2 influenza vaccine doses).
[b] Group 1 will receive a 0.25-mL dose of Fluzone Quadrivalent vaccine at Day 0; Group 2 will receive a 0.5-mL dose of Fluzone Quadrivalent vaccine at Day 0.
[c] One or 2 doses of influenza vaccine will be administered according to the Advisory Committee on Immunization Practices guidance in effect during the study. If 2 doses of influenza vaccine are indicated, 1 dose will be administered during Visit 1 and the second dose (of the same volume as the first dose) will be administered approximately 28 days later during Visit 2.
[d] The subject's parent/guardian will be contacted by telephone on Day 8 after vaccination as a reminder to complete the diary card and to bring it with them to the next visit.
[e] The termination form will be completed at Visit 2 for subjects receiving 1 dose of influenza vaccine or at Visit 3 for subjects receiving 2 doses of influenza vaccine.

4 Endpoints and Assessment Methods

4.1 Primary Endpoint and Assessment Methods

4.1.1 Primary Safety Endpoint - Body Temperature

The primary (safety) objective is presented in Section 2.1.

Rates of any fever (temperature ≥ 100.4°F [38.0°C]) during the 7 days after either vaccination (Dose 1 and Dose 2 combined) in each vaccine group.

4.1.2 Body Temperature Measurement Methods and Assessment

After each vaccination, the subject's parent/guardian will be provided with a safety diary card and will be instructed how to use them.

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 diary card, and the highest temperature will be recorded by the site in the electronic case report form (eCRF) for every day (Day 0 to Day 7). The preferred route for temperature measurement in this trial is rectal. In cases where a rectal temperature cannot be obtained, a non-preferred route (e.g., axillary) may be used. Pre-vaccination temperature is also to be systematically collected by the Investigator in the eCRF for all subjects. Tympanic thermometers must not be used.

All body temperatures reported as < 90°F will be transformed / set as missing except those temperatures identified as having been reported in degrees Celsius (°C). Temperatures reported in °C will be transformed into degrees Fahrenheit (°F) using the formula:

$$(\text{Temperature (°C)} \times (9/5)) + 32 = \text{Temperature (°F)}$$

The primary endpoint of fever during the solicited period (Day 0 to Day 7) will be derived based on a conservative approach, as follows:

- If at least 1 of the daily measurements is ≥100.4°F, then the value of fever=Yes
- If one or more days during the solicited period have non-missing body temperatures that are all < 100.4°F AND the parent/guardian of the subject answered "No" to the presence of fever, then the value of fever=No
- If all days during the solicited period have missing body temperatures, then the value of fever=Missing, even if the parent/guardian of the subject answered "No" to the presence of fever

4.2 Secondary Endpoints and Assessment Methods

The secondary immunogenicity objective is presented in Section 2.2.

4.2.1 Immunogenicity Endpoints

- Geometric mean titers (GMTs): The hemagglutination inhibition (HAI) GMTs (for each of the 4 virus strains) at 28 days after the final vaccination.
- Seroconversion rates: The percentages of subjects with either a pre-vaccination titer < 10 (1/dil) and a post-vaccination titer ≥ 40 (1/dil), or a pre-vaccination titer ≥ 10 (1/dil) and a ≥ 4-fold increase in post-vaccination titer at 28 days after the final vaccination.

4.2.2 Immunogenicity Assessment Methods

Antibodies to Influenza Viruses

Anti-influenza antibodies will be measured by HAI performed by Sanofi Pasteur's Global Clinical Immunology (GCI) department or an external testing laboratory under GCI's supervision. Serum samples and quality control sera (sheep and/or human sera) will be incubated with Sigma Type III NA (receptor-destroying enzyme, neuraminidase type III from *Vibrio cholerae*) to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins will be performed by incubating the serum samples and quality control sera with a red blood cell (RBC) suspension. Following this, the mixtures will be centrifuged and the supernatants containing the treated sera will be collected for testing. Ten 2-fold dilutions (starting at 1/10) of the treated serum samples and quality control sera will be incubated with a previously titrated influenza virus solution at a concentration of 4 hemagglutination unit (HAU)/25 µL. Influenza virus solution will not be added to the serum control wells containing only serum and RBCs. The mixture will be incubated and a RBC suspension will be added. Following incubation, the results will be read. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. Each serum sample will be titrated in independent duplicates, and the 2 values, which do not differ by more than one 2-fold dilution, will be reported. The GMT between the 2 values will be calculated after the release of the data to the Clinical Data Management (CDM) platform. The lower limit of quantification (LLOQ) for HAI is set at 10, the lowest serum dilution used in the assay i.e., 1/10. Titers below this level are reported as < 10.

4.3 Observational Endpoints and Assessment Methods

4.3.1 Safety

The observational safety objective is presented in Section 2.3.1.

4.3.1.1 Safety Definitions

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

Adverse Event:

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:

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

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability/incapacity[c]

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

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

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

- Is a congenital anomaly/birth defect
- Is an important medical event[a]

Additionally, the following important medical events are to be considered as SAEs:

- New onset of Guillain-Barré syndrome (GBS), encephalitis/myelitis (including transverse myelitis), neuritis (including Bell's palsy, optic neuritis, and brachial neuritis), thrombocytopenia, vasculitis, convulsions (including febrile convulsions), and anaphylaxis or other hypersensitivity/allergic reactions

Adverse Reaction:

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

(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:

An unexpected AR 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 eCRF. The assessment of these AEs post-vaccination is mandatory. A solicited reaction is defined by a combination of:

- Symptom and
- Onset post-vaccination

Examples of solicited reactions include injection site pain between Day 0 and Day 7 post-vaccination, or headache between Day 0 and Day 7.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the eCRF 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 eCRF in terms of diagnosis and/or onset post-vaccination. For example, if headache between Day 0 and

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[a] 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, the development of drug dependency or drug abuse, or new-onset diabetes or autoimmune disease.

Day 7 is a solicited reaction (i.e., prelisted in the eCRF), then a headache starting on Day 7 is a solicited reaction, whereas headache starting on Day 8 post-vaccination is an unsolicited AE.

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

Injection Site Reaction:

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

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).

Adverse Events of Special Interest:

AEs of special interest are AEs that are considered by the Sponsor to be relevant for the monitoring of the safety profile of the investigational vaccine.

4.3.1.2 Safety Endpoints

The observational endpoints for the evaluation of safety are:

1) Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 20 minutes after each vaccination.
2) Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited injection site reactions (prelisted in the subject's diary card and eCRF) occurring between Day 0 and Day 7 after each vaccination.
3) Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited systemic reactions (prelisted in the subject's diary card and eCRF) occurring between Day 0 and Day 7 after each vaccination.
4) Occurrence, nature (MedDRA PT), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs between Visit 1 and Visit 2 for subjects receiving 1 dose or between Visit 1 and Visit 3 for subjects receiving 2 doses.
5) Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the study, of SAEs between Visit 1 and Visit 2 for subjects receiving 1 dose or between Visit 1 and Visit 3 for subjects receiving 2 doses.

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

Adverse events of special interest will be captured as SAEs. These include new onset of GBS, encephalitis/myelitis (including transverse myelitis), neuritis (including Bell's palsy, optic neuritis, and brachial neuritis), thrombocytopenia, vasculitis, convulsions (including febrile convulsions), and anaphylaxis or other hypersensitivity/allergic reactions between Visit 1 and Visit 2 for subjects receiving 1 dose, or between Visit 1 and Visit 3 for subjects receiving 2 doses.

4.3.1.3 Safety Assessment Methods

See Section 9.3.1.3 of the protocol version 2.0, 13 June 2016.

4.3.2 Immunogenicity

The observational immunogenicity objective is presented in Section 2.3.2.

4.3.2.1 Immunogenicity Endpoints

Immunogenicity will be evaluated in a subset of approximately 1600 randomly selected subjects prior to vaccination on Day 0 (Visit 1) and at 28 (window, 28–35) days after the final vaccination using the HAI technique. For each influenza vaccine strain, HAI assay titers at pre-vaccination (Day 0) and at 28 (window, 28–35) days after the final vaccination will be determined in duplicate.

The derived endpoints are:

- Geometric means of HAI assay titers for individual subjects at pre-vaccination (Day 0) and at 28 (window, 28–35) days after the final vaccination.
- Ratios of individual post-final vaccination titers divided by individual pre-vaccination titers.
- Seroprotection: subjects with a titer $\geq$ 40 (l/dil) at pre-vaccination or at 28 (window, 28–35) days after the final vaccination.
- Seroconversion: subjects with either a pre-vaccination titer $<$ 10 (1/dil) and a post-vaccination titer $\geq$ 40 (1/dil), or a pre-vaccination titer $\geq$ 10 (1/dil) and a $\geq$ 4-fold increase in post-vaccination titer at 28 (window, 28–35) days after the final vaccination.

4.3.2.2 Immunogenicity Assessment Methods

The immunogenicity assessment methods are presented in Section 4.2.2.

4.4 Derived Endpoints: Calculation and Derivation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

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

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

1) For solicited reactions (except fever/pyrexia) for which an Investigator records their presence as "No" and for which all daily records are missing, all daily intensities will be derived as None

2) For a temperature with partially missing data (MD) after the decimal point, the data will be analyzed by replacing "MD" with zero. For example, a "39.MD°C" daily temperature will be considered as "39.0°C" in the analysis

3) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions, the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3

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

4.4.1.1.2 Maximum Overall Intensity

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

4.4.1.1.3 Presence

Presence will be derived from the maximum overall intensity during the period considered:

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

Subjects with at least 1 non-missing presence for a specific endpoint will be included in the analysis. Conversely, those with all missing presence will not be included in the analysis of the endpoint.

4.4.1.1.4 Time of Onset

Time of onset will be derived from the daily intensities computed as described in Section 4.4.1.1.1. It will correspond to the first day with intensity of Grade 1, Grade 2, or Grade 3. Note: If a reaction is not continuous (i.e., reaction occurs during 2 separate periods of time intervened by at least 1 daily intensity of Missing or None) then the time of onset is the first day of the first occurrence. For subjects who received 2 doses, the worst-case scenario will be used for the post-any dose summary (i.e., the smaller time of onset [latency] period will be used if present for both doses, or the available time of onset [latency] period will be used if present for either dose).

Note: Unsolicited non-serious AEs that occur before vaccination (i.e., those with a negative time of onset) will not be included in the analysis, but will be listed separately.

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence during the period considered will be derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. The number of days of occurrence during the solicited period with a specified intensity may also be derived. For subjects who received 2 doses, the worst case-scenario will be used for the post any dose summary (i.e., the larger number of days will be used if present for both doses, or the available number of days will be used if present for either dose).

4.4.1.1.6 Overall Number of Days of Occurrence

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

> (stop date - last vaccination date) + (number of days of occurrence within the solicited period) - length of the solicited period + 1

If the stop date is missing or incomplete (contains MD), the overall number of days of occurrence will be considered as Missing. For subjects who received 2 doses, the worst-case scenario will be used for the post-any dose summary (i.e., the larger number of days will be used if present for both doses, or the available number of days will be used if present for either dose).

4.4.1.1.7 Ongoing

Ongoing will be derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 and the maximum intensity during the ongoing period. The Investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

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

4.4.1.2 Unsolicited Non-serious AEs

4.4.1.2.1 Intensity

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

If the unsolicited non-serious AE is measurable and its MedDRA PT is part of the list of solicited reactions, then the measurement will be derived based upon and following the same rule as the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Intensity for the other unsolicited non-serious AEs will correspond to the value reported in the eCRF.

The maximum intensity will correspond to the highest intensity for a unique term.**Last Vaccination**

The last vaccination before an unsolicited non-serious AE is derived from the visit numbers provided in the clinical database and will be calculated as follows:

- If an unsolicited non-serious AE has a non-missing visit number, the visit number will be used to determine the last vaccination before the unsolicited non-serious AE
- If the visit number is missing, then the start date of the unsolicited non-serious AE will be used to determine the last vaccination before the unsolicited non-serious AE

4.4.1.2.3 Time of Onset

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

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

The time of onset will be considered as missing only if 1 or both of the dates are missing or partially missing.

Adverse events with a missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number and will be included in tables. For subjects who received 2 doses, the worst-case scenario will be used for the post-any dose summary (i.e., the smaller time of onset [latency] period will be used if present for both doses or the available time of onset [latency] period will be used if present for either dose).

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

4.4.1.2.4 Duration

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

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

The duration will be considered as missing only if 1 or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing. For subjects who received 2 doses, the worst-case scenario will be used for the post-any dose summary (i.e., the longer duration will be used if present for both doses or the available duration will be used if present for either dose).

4.4.1.3 Serious Adverse Events

4.4.1.3.1 Last Vaccination

The last vaccination before an SAE will be derived from the last visit number provided in the clinical database and will be calculated as follows:

- If an SAE has a non-missing visit number, the visit number will be used to determine the last vaccination before the SAE
- If the visit number is missing, then the start date of the SAE will be used to determine the last vaccination before the SAE

4.4.1.3.2 Time of Onset

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

4.4.1.3.3 Duration

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

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

To appropriately manage extreme values (< LLOQ and ≥ ULOQ [upper limit of quantification]) for analysis purposes, the following computational rules will be applied to the values provided in the clinical database for each blood sample drawn, as appropriate:

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

4.4.2.2 Seroprotection

If the computed value is ≥ 40 (1/dil) at pre-vaccination and at post-final vaccination, then the derived seroprotection indicator will be "Yes" for that test, otherwise seroprotection will be "No".

Note: If the computed value is missing, seroprotection will be missing.[redacted]

[redacted]

4.4.2.4 Seroconversion

If a pre-vaccination titer is < 10 (1/dil) and a post-final vaccination titer is ≥ 40 (1/dil), or a pre-vaccination titer is ≥ 10 (1/dil) and there is a ≥ 4-fold increase in post-final vaccination titer, then the derived seroconversion indicator will be "Yes" for that test, otherwise seroconversion will be set to "No".

4.4.3 Efficacy

Not applicable.

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

To calculate age at enrollment, the following algorithm will be used:

- The difference in years will be calculated by subtracting the year of birth from the year of the enrollment visit; this difference will be multiplied by 12 to get the difference in months
- The month of birth will be subtracted from the month of the enrollment visit
- The values calculated above will be added to obtain a provisional age in months
- It will be determined when the day of the enrollment visit (e.g., the 31st day of the month) occurred relative to the day of birth (e.g., the 28th day of the month). The final age in months will be determined as follows:

a) If the day of the enrollment visit ≥ day of birth, then the sum calculated above will be considered the final age in months; otherwise,
b) If the day of the enrollment visit < day of birth, then the sum calculated above will be reduced by 1 month to obtain the final age in months

4.4.4.2 Duration of a Subject's Participation in the Trial

The duration of a subject's participation in the study will be computed as follows:

maximum date (of visit, of termination form) - date of Visit 1 +1.

4.4.4.3 Duration of the Study

The duration of the study will be computed as follows:

maximum date (of visit, of termination form) of all subjects －minimum date of Visit 1 for all subjects +1.

5 Statistical Methods and Determination of Sample Size

The statistical analyses of the data will be performed under the responsibility of the Sanofi Pasteur Biostatistics and Programming platform using SAS® Version 9.2 software or later.

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

The distribution of the subjects enrolled into the study will be summarized by investigative site and enrollment group. A description of the populations will be presented. The number of subjects enrolled, age at enrollment (mean, median, minimum, and maximum), sex, and ethnic origin and racial origin will be summarized, as well as the number and description of protocol violations will be presented.

Continuous variables will be presented by summary statistics (e.g., mean and standard deviation [SD]) for the non-immunogenicity endpoints; geometric means (GMs) and their confidence intervals (CIs) for the immunogenicity endpoints), and the categorical variables will be presented by frequency distributions (frequency counts, percentages, and their CIs for the main endpoints).

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive Statistics Produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects Percentage of subjects
	Continuous data	Mean, SD, quartiles, minimum, and maximum
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs) of subjects Unsolicited: Number and percentage (95% CIs) of subjects, and number of events

	Continuous data	Mean, SD, quartiles, minimum, and maximum
Immunogenicity results	**Categorical data (seroprotection, seroconversion, cutoff)**	Number and percentage of subjects, and 95% CI
	Continuous data (titer data and fold-rise)	log10: Mean and SD Anti-log_{10} (work on log_{10} distribution, and anti-log_{10} applied): GM, 95% CI of the GM, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve

CI: confidence interval; GM: geometric mean; SD: standard deviation

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (3), i.e., using the inverse of the beta integral in SAS®.

For immunogenicity results, assuming that log_{10} transformation of the titers follows a normal distribution, at first, the mean and the 95% CI will be calculated on log10 (titers/data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide GMs and their 95% CI.

Rounding rules on descriptive statistics edited will follow the Sanofi Pasteur standard working instruction ("Conventions for the Presentation of Descriptive Statistics"). To present percentages (and 95% CIs of percentages), 1 digit after the decimal place will be used unless indicated otherwise.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

The Safety Analysis Set (SafAS) population will be used to establish non-inferiority for the primary objective.

5.1.1.1 Hypotheses

During the 7 days after either vaccination (Dose 1 and Dose 2 combined), the 0.5-mL dose of Fluzone Quadrivalent vaccine will be non-inferior to the 0.25-mL dose of Fluzone Quadrivalent vaccine in terms of fever reaction (temperature ≥ 100.4°F [38.0°C]) in subjects 6 to < 36 months of age. The null and alternative hypotheses are:

$$H_0: P_{0.5mL} - P_{0.25mL} \geq 5\%$$

$$H_A: P_{0.5mL} - P_{0.25mL} < 5\%$$

Where:

$P_{0.25mL}$ = percentage of subjects with fever reaction (temperature ≥ 100.4°F [38.0°C]) after vaccination with the first dose and/or the second dose of 0.25-mL Fluzone Quadrivalent vaccine.

$P_{0.5mL}$ = percentage of subjects with fever reaction (temperature ≥ 100.4°F [38.0°C]) after vaccination with the first dose and/or the second dose of 0.5-mL Fluzone Quadrivalent vaccine.

5.1.1.2 Statistical Methods

The 0.5-mL dose of Fluzone Quadrivalent vaccine will be demonstrated as non-inferior to the 0.25-mL dose of Fluzone Quadrivalent vaccine in terms of fever reaction through an assessment of the rates of any fever (temperature ≥ 100.4°F [38.0°C]) during the day of vaccination or during the 7 days following any dose (Dose 1 and Dose 2 combined).

Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% CI of the rate difference between Group 2 (subjects receiving 0.5 mL of vaccine) and Group 1 (subjects receiving 0.25 mL of vaccine) is < 5%. The 95% CI of the difference in proportions $P_{0.5mL} - P_{0.25mL}$ will be computed using the Wilson Score method without continuity correction as quoted by Newcombe (3).

To test this hypothesis, a 2-sided 95% CI will be constructed around the difference, $P_{0.5mL} - P_{0.25mL}$, where $P_{0.25mL}$ and $P_{0.5mL}$ are the proportions of subjects in Group 1 and Group 2, respectively, experiencing any fever (temperature ≥ 100.4°F [38.0°C]) during the day of vaccination or during the 7 days following any dose (Dose 1 and Dose 2 combined).

The hypothesis will be supported by the data, if the upper bound of the calculated 95% CI is < 5%. This is the equivalent to testing the null hypothesis using a 1-sided type I error rate of 0.025.

$$H_0: P_{0.5mL} - P_{0.25mL} \geq 5\%$$

$$H_A: P_{0.5mL} - P_{0.25mL} < 5\%$$

If the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Because of concerns regarding the integrity of safety data collected at Site 009, an additional statistical analysis will be conducted that excludes temperature data collected at this site. The results of this analysis will be reported in the CSR appendices.

Nevertheless, the study conclusion (non-inferiority with respect to the proportion of subjects with fever in Group 1 vs Group 2) will be based on the primary analysis that includes data from Site 009.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

The Per-Protocol Analysis Set (PPAS) will be used as the primary analysis set for the secondary objectives.

5.1.2.1 Hypotheses

5.1.2.1.1 Geometric Mean Titers

For each of the 4 virus strains, the post-final vaccination GMTs in subjects 6 to < 36 months of age who receive the 0.5-mL dose of Fluzone Quadrivalent vaccine will be non-inferior to the post-final vaccination GMTs in those subjects who receive the 0.25-mL dose of Fluzone Quadrivalent vaccine.

5.1.2.1.2 Seroconversion

For each of the 4 virus strains (A/H1N1, A/H3N2, B1 and B2), the seroconversion rates in subjects 6 to < 36 months of age who receive the 0.5-mL dose of Fluzone Quadrivalent vaccine will be non-inferior to the seroconversion rates in those subjects who receive the 0.25-mL dose of Fluzone Quadrivalent vaccine.

5.1.2.2 Statistical Methods

5.1.2.2.1 Geometric Mean Titers

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs (0.5-mL dose divided by 0.25-mL dose) at 28 (window, 28–35) days after the final vaccination.

Non-inferiority for GMTs will be demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio is > 0.667 for each of the 4 virus strains (A/H1N1, A/H3N2, B1 and B2). The 95% CI will be calculated using normal approximation of log-transformed titers.

For the separately virus strain (A/H1N1, A/H3N2, B1 and B2), the primary parameter will be the difference of the means of the log10-transformed post-vaccination titers between $GMT_{0.5mL}$ and $GMT_{0.25mL}$.

Each hypothesis will be supported by the data if the upper bound of the calculated 95% CI is > 0.667. This is the equivalent to testing the null hypothesis using a 1-sided type I error rate of 0.025.

For each virus strain (A/H1N1, A/H3N2, B1 and B2), the null hypothesis and the alternative hypothesis, are:

$$H_0: GMT_{0.5mL} / GMT_{0.25mL} \leq 0.667$$

$$H_A: GMT_{0.5mL} / GMT_{0.25mL} > 0.667$$

or equivalently,

$$H_0: \log_{10}(GMT_{0.5mL}) - \log_{10}(GMT_{0.25mL}) \leq \log_{10}(0.667)$$

$$H_A: \log_{10}(GMT_{0.5mL}) - \log_{10}(GMT_{0.25mL}) > \log_{10}(0.667)$$

For the separately considered GMT hypotheses, if the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

The 2-sided 95% CI for the ratio of GMTs ($GMT_{0.5mL} / GMT_{0.25mL}$) will be calculated using normal approximation of log-transformed concentrations.

The 95% CI for the GMT ratio between 2 groups will be constructed as follows: Logarithm transformation of the individual concentrations will be calculated. Assuming that individual $\log_{10}$ (concentration) is normally distributed, the 95% CI for the difference in $\log_{10}$ (GMT) between 0.5-mL (or Group$_i$) and 0.25-mL (or Group$_j$) will be in the form:

$$\bar{X}_i - \bar{X}_j \pm t(1-\alpha/2, n_i + n_j - 2) \times S\sqrt{1/n_i + 1/n_j}$$

where $\bar{X}_i = \log_{10}(\text{GMC})$ is the mean of $\log_{10}$ (concentration) of Group i,

$S^2 = [(n_i - 1)\, S_i^2 + (n_j - 1)\, S_j^2] / (n_i + n_j - 2)$ is the pooled sample variance,

n_i and S_i^2 are the sample size and sample variance of Group i,

$t(1-\alpha/2,\ n_i + n_j - 2)$ is the $100(1-\alpha/2)$ percentile of the t-distribution with degrees of freedom $df = n_i + n_j - 2$.

For descriptive purposes, the statistics presented in Table 5.1 will be produced.

5.1.2.2.2 Seroconversion

The statistical methodology will be based on a 2-sided 95% CI of the difference in seroconversion rates (0.5-mL dose minus 0.25-mL dose) at 28 (window, 28–35) days after the final vaccination. Non-inferiority for seroconversion will be demonstrated if the lower limit of the 2-sided 95% CI is > -10% for the 4 strains (A/H1N1, A/H3N2, B1 and B2). The 95% CI of the rate difference will be computed using the Wilson Score method without continuity correction.
For each virus strain (A/H1N1, A/H3N2, B1 and B2), the null hypothesis and the alternative hypothesis, are:

H_0: $P_{0.5mL} - P_{0.25mL} \leq -10\%$

H_A: $P_{0.5mL} - P_{0.25mL} > -10\%$

For the separately considered seroconversion hypotheses, if the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

The CI of the difference in proportions $P_{0.5mL} - P_{0.25mL}$ will be computed using the Wilson Score method without continuity correction, quoted by Newcombe (3).

For descriptive purposes, the statistics presented in Table 5.1 will be produced.

5.1.3 Statistical Methods for Observational Objectives

For the main safety and immunogenicity parameters, 95% CIs of point estimates will be calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions.

5.1.3.1 Safety Analysis

The safety analysis will report the occurrence of solicited reactions and the incidence of unsolicited AEs between Visit 1 and Visit 2 (or between Visit 1 and Visit 3 for those subjects receiving 2 doses).

To avoid any under-estimation of the incidences, the number of subjects with documented safety will be used as denominator for the frequencies.

- For solicited reactions, the denominator will be the total number of subjects who have non-missing data for the endpoint considered
- For unsolicited AEs, the denominator will be the total number of subjects who were vaccinated at the dose analyzed.

The safety tables will be produced using a subject approach, i.e., number of subjects who experienced at least 1 safety event during a considered period.

The 2-sided 95% CIs for the percentages will be calculated using the exact binomial method (Clopper-Pearson method).

Additional safety tables, which will be based on analyses that exclude safety data from Site 009, will be presented in the CSR appendices. Specifically, these tables will be those that provide overall safety overviews/summaries and those that describe solicited reactions after any vaccination by maximum intensity.

Solicited reactions

The solicited injection site reactions and the solicited systemic reactions will be presented separately (except in summary tables).

Solicited reactions will be presented according to their nature (MedDRA [19.0] PT), intensity (Grade 1, 2, or 3), time of onset, and number of days of occurrence.

Unsolicited AEs

Unsolicited AEs included in the analysis will be summarized in the safety overview and analyzed according to their nature (MedDRA [19.0] system organ class and PT classification) and relationship to the vaccination.

Injection Site Reactions

For each treatment group, the number and percentage of subjects experiencing any injection site reaction after injection will be calculated.

The description of injection site reactions will be presented according to:

- Solicited injection site reactions

  All solicited injection site reactions that occur each day within 7 days after injection will be analyzed.

- Unsolicited injection site reactions

- All unsolicited injection site reactions between Visit 1 and Visit 2 (or between Visit 1 and Visit 3 for those subjects receiving 2 doses) will be described according to the type of events.

Systemic Events and Reactions

For each treatment group, the number and percentage of subjects experiencing any unsolicited immediate systemic event in the 20 minutes after injection will be calculated.

In addition, the description of systemic events will be structured according to:

- Solicited systemic reactions

  All solicited systemic reactions that occur each day within 7 days after injection will be analyzed.

- Unsolicited systemic events

  All unsolicited systemic events between Visit 1 and Visit 2 (or between Visit 1 and Visit 3 for those subjects receiving 2 doses) will be described according to the type of events.

Serious Adverse Events

The number and percentage of subjects with SAEs after vaccination within 28 days after each vaccination in each treatment group will be calculated by outcome, seriousness, and relationship to vaccination.

5.1.3.2 Immunogenicity Analysis

The following immunogenicity parameters will be calculated for each influenza strain with 95% CIs of point estimates calculated using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation for GMTs:

- Geometric mean HAI assay titers at pre-vaccination (Day 0) and at 28 (window, 28–35) days after the final vaccination.
- Geometric means of the individual titer ratios of post-final vaccination/pre-vaccination.
- Seroprotection rates: The percentages of subjects with a titer $\geq$ 40 (1/dil) at pre-vaccination and at 28 (window, 28–35) days after the final vaccination.
- Seroconversion rates: The percentages of subjects with either a pre-vaccination titer $<$ 10 (1/dil) and a post-vaccination titer $\geq$ 40 (1/dil), or a pre-vaccination titer $\geq$ 10 (1/dil) and a $\geq$ 4-fold increase in post-vaccination titer at 28 (window, 28–35) days after the final vaccination.

[redacted]

5.2 Analysis Sets

Three analysis sets will be used: The SafAS, the FAS, and the PPAS.

5.2.1 Safety Analysis Set

The SafAS is defined as those subjects who have received study vaccine.

5.2.2 Full Analysis Set

[redacted]

5.2.3 Per-Protocol Analysis Set

[redacted]

- Subject did not meet all protocol-specified inclusion criteria or met at least 1 of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule as per protocol
- Subject received a vaccine dose other than the one that he/she was randomly assigned to receive
- Preparation and/or administration of vaccine was not done as per protocol
- For subjects receiving 2 doses of vaccine, subject did not receive the second dose within the proper time window (28–35 days after the first vaccination)
- Subject did not provide a post-dose serology sample in the proper time window (28–35 days) after the final vaccination or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy/medication/vaccine that might impact antibody response to the study vaccine
- Subject's post-vaccination serology sample did not produce a valid HAI test result for any strain
- Any other deviation identified during conduct of the study conduct and judged by the clinical team during data review as having a potential impact on the assessment of immunogenicity
- Other protocol deviations that will result in the exclusion of a subject from the per-protocol analysis set include:
    - Re-randomization of a subject
    - Inclusion in the immunogenicity subset after not being assigned to the subset originally
    - Receipt of study vaccine not corresponding to the medication ID assigned to the subject

5.2.4 Populations Used in Analyses

Baseline and demographic analyses will be performed on SafAS, FAS and PPAS.

The safety analyses will be performed on the SafAS.

The analysis of the primary endpoint, rate of fever (temperature ≥ 100.4°F [38.0°C]), is based on fever caused by either vaccination (Dose 1 and Dose 2 combined).

All subjects will have their safety analyzed after any dose according to the vaccine they actually received at the first dose. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

The immunogenicity analyses will be performed on both the FAS and PPAS. The PPAS will be the primary analysis set for assessing non-inferiority by immunogenicity.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

No replacement of missing data will be done. All subjects with safety data and all safety data recorded in the eCRFs will be included in the safety analyses. No search for outliers will be performed.

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

5.3.1.1 Immediate

For unsolicited non-serious systemic AEs, a missing response to the “Immediate” field is assumed to have occurred after the 20-minute surveillance period and will not be imputed.

5.3.1.2 Causality

Unsolicited AEs and SAEs with missing causality will be considered as related to vaccination.

5.3.1.3 Measurements

Missing measurements (for temperature or length) will remain missing and will not be imputed. Nevertheless, the following rule will be applied: If the measurement (temperature or length) is missing the value after the decimal point, the data will be analyzed by replacing “MD” with zero. For example, a “102.MD°F” daily temperature will be considered as “102.0°F” during the analysis.

5.3.1.4 Intensity

No replacement of the missing qualifier will be done. For analysis, the missing class for the AE qualifier will be provided in the descriptive tables.

5.3.1.5 Start Date and Stop Date

No replacement of missing dates will be performed.

For instance:

- If the onset of an AE cannot be calculated due to a missing start date, then the onset will be considered as missing
- If the stop date of an unsolicited AE is missing, then the duration of that AE will be considered as missing
- If the stop date of a solicited reaction continuing after the solicited period is missing or incomplete, then the number of days of occurrence of that solicited event will be considered as missing

All missing and partially missing dates will be listed where appropriate.

5.3.2 Immunogenicity

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

5.4 Interim/Preliminary Analysis

No planned interim/preliminary analyses are planned.

5.5 Determination of Sample Size and Power Calculation

[redacted]

5.6 Data Review for Statistical Purposes

A review of the data is anticipated through the data review process led by CDM before database lock.

5.7 Changes in the Conduct of the Trial or Planned Analyses

Not applicable.

6 Statistical Analysis Plan TLF Shells

The second part of the SAP (in a separate file) describes the tables, listings, and figures that are planned to be included in the CSR, as well as other outputs for internal purpose only.

This document (SAP core body part), and formal review/approval includes also the following document:

SAP - TLF part (at the time of review/approval)	
CLI number:	CLI_1684182
Version and date:	Version 1.0 – 2017

7 References List

1. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices-United States, 2013-14. MMWR. 2013;62(RR07):1-43.Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP) -- United States, 2014-15 influenza season. MMWR. 2014;63(32):691-7.
3. Newcombe R.G., Two-sided confidence intervals for the single proportion: comparison of seven methods, Stat Med. 1998;17:857-72.