**Protocol C3671004**

# A PHASE 2B, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE WHEN ADMINISTERED CONCOMITANTLY WITH TETANUS, DIPHTHERIA, AND ACELLULAR PERTUSSIS VACCINE (TDAP) IN HEALTHY NONPREGNANT WOMEN 18 THROUGH 49 YEARS OF AGE

**Statistical Analysis Plan**
**(SAP)**

**Version:** 2 (Amendment 1)

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**Date:** 08 Nov 2019



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## APPENDICES

## 1. VERSION HISTORY

**Table 1. Summary of Changes**

| Version (Amendment)/ Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| 1/ 23 Aug 2019 | Original/ 21 Jun 2019 | N/A | N/A |
| 2 (Amendment 1)/ 08 Nov 2019 | Protocol Amendment 1/ 17 Sep 2019 | Revised to include changes from protocol Amendment 1 | • Updated the author's job title.<br>• Added the secondary objective (Section 2.1.2).<br>• Updated Section 2.1.4 to reference the secondary objective.<br>• Updated Section 2.2 with the increased sample size and references to sterile water for injection (sWFI).<br>• Added the secondary endpoint in Section 3.2.<br>• Updated Section 5.1 to include a reference to the secondary objective.<br>• Added Section 6.2.1 corresponding to the secondary endpoint.<br>• Updated the visit window for the 1-month visit to be consistent with other studies in the program. |

## 2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3671004. A brief description of the study design and the study objectives is given below. Subsequent sections describe analysis populations and give the definitions of the safety and immunogenicity endpoints followed by details of statistical reporting. A list of tables, listings, and figures, mock-up tables, and programming rules are prepared separately based on the methods described in this document. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

## 2.1. Study Objectives, Endpoints, and Estimands

### 2.1.1. Primary Objectives

- To demonstrate that the immune responses induced by tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) when administered concomitantly with the respiratory syncytial virus (RSV) vaccine (RSV vaccine + Tdap) are noninferior to the immune responses induced by Tdap alone (placebo + Tdap).

- To demonstrate that the immune responses induced by the RSV vaccine (RSV A and B antigens) when administered concomitantly with Tdap (RSV vaccine + Tdap) are noninferior to the immune responses induced by the RSV vaccine alone (RSV vaccine + placebo).

- To evaluate the acceptability of the safety and tolerability profile of the RSV vaccine when administered concomitantly with Tdap and when RSV vaccine is administered alone.

### 2.1.2. Secondary Objectives

- To demonstrate that the immune responses induced by the RSV vaccine (RSV A and B antigens) when administered concomitantly with Tdap (RSV vaccine + Tdap) are noninferior (using a 1.5-fold margin) to the immune responses induced by the RSV vaccine alone (RSV vaccine + placebo).

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### 2.1.4. Primary and Secondary Estimands

- **Difference in percentage of participants with anti–tetanus toxoid antibody concentrations ≥0.1 IU/mL between the combined RSV vaccine + Tdap groups and the placebo + Tdap group.**

This estimand includes the following 4 attributes:

  - Population: Participants receiving all doses of investigational products and in compliance with key protocol criteria (evaluable participants).

  - Variable: Presence of anti–tetanus toxoid antibody concentrations ≥0.1 IU/mL at 1 month after vaccination.

  - Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored.

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Missing serology results will not be imputed, as missing completely at random (MCAR) is assumed.

- Population-level summary: Difference (and 95% confidence interval [CI]) in the percentage of participants with anti–tetanus toxoid antibody concentrations ≥0.1 IU/mL between the combined RSV vaccine + Tdap groups and the placebo + Tdap group.

- **Difference in percentage of participants with anti–diphtheria toxoid antibody concentrations ≥0.1 IU/mL between the combined RSV vaccine + Tdap groups and the placebo + Tdap group.**

This estimand includes the following 4 attributes:

- Population: Participants receiving all doses of investigational products and in compliance with key protocol criteria (evaluable participants).

- Variable: Presence of anti–diphtheria toxoid antibody concentrations ≥0.1 IU/mL at 1 month after vaccination.

- Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Missing serology results will not be imputed, as MCAR is assumed.

- Population-level summary: Difference (and 95% CI) in the percentage of participants with anti–diphtheria toxoid antibody concentrations ≥0.1 IU/mL between the combined RSV vaccine + Tdap groups and the placebo + Tdap group.

- **Geometric mean ratio (GMR) of anti–pertussis toxin (anti-PT) antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group.**

This estimand includes the following 4 attributes:

- Population: Participants receiving all doses of investigational products and in compliance with key protocol criteria (evaluable participants).

- Variable: Anti-PT antibody concentrations at 1 month after vaccination.

- Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Missing serology results will not be imputed, as MCAR is assumed.

- Population-level summary: GMR estimated by the ratio of the geometric mean concentration (GMC) of anti-PT antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group.

- **GMR of anti–filamentous hemagglutinin (anti-FHA) antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group.**

This estimand includes the following 4 attributes:

  - Population: Participants receiving all doses of investigational products and in compliance with key protocol criteria (evaluable participants).
  - Variable: Anti-FHA antibody concentrations at 1 month after vaccination.
  - Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Missing serology results will not be imputed, as MCAR is assumed.
  - Population-level summary: GMR, estimated by the ratio of the GMC of anti-FHA antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group.

- **GMR of antipertactin (anti-PRN) antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group.**

This estimand includes the following 4 attributes:

  - Population: Participants receiving all doses of investigational products and in compliance with key protocol criteria (evaluable participants).
  - Variable: Anti-PRN antibody concentrations at 1 month after vaccination.
  - Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Missing serology results will not be imputed, as MCAR is assumed.
  - Population-level summary: GMR, estimated by the ratio of the GMC of anti-PRN antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group.

- **GMR of the geometric mean titer (GMT) for RSV A– and RSV B–neutralizing antibody titers from the combined RSV vaccine + Tdap groups to the combined RSV vaccine + placebo group.**

This estimand is defined according to the primary and secondary objectives, is in alignment with the primary and secondary endpoints, and includes the following 4 attributes:

  - Population: Participants receiving all doses of investigational products and in compliance with key protocol criteria (evaluable participants).
  - Variable: Antibody titers at 1 month after vaccination.

- Intercurrent event(s): For participants who discontinue or have major protocol violations, all postdiscontinuation or postviolation observations will be censored. Missing serology results will not be imputed, as MCAR is assumed.

- Population-level summary: GMR, estimated by the ratio of the GMT for RSV A– and RSV B–neutralizing antibody titers from the combined RSV vaccine + Tdap groups to the placebo + Tdap group.

- **Percentage of participants reporting local reactions.**

This estimand includes the following 4 attributes:

- Population: Participants who receive 1 dose of investigational product.

- Variable: Presence/absence of prespecified local reactions within 7 days after vaccination.

- Intercurrent event(s): For participants who discontinue, all collected data will be included. Missing data will not be imputed.

- Population-level summary: Percentage of participants reporting local reactions in each vaccine group.

- **Percentage of participants reporting systemic events.**

This estimand includes the following 4 attributes:

- Population: Participants who receive 1 dose of investigational product.

- Variable: Presence/absence of prespecified systemic events within 7 days after vaccination.

- Intercurrent event(s): For participants who discontinue, all collected data will be included. Missing data will not be imputed.

- Population-level summary: Percentage of participants reporting systemic events in each vaccine group.

- **Percentage of participants reporting adverse events (AEs) from the time of vaccination through 1 month after vaccination.**

This estimand includes the following 4 attributes:

- Population: Participants who receive 1 dose of investigational product.

- Variable: Presence of AEs within 1 month after vaccination.

- Intercurrent event(s): For participants who discontinue, all collected data will be included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

- Population-level summary: Number and percentage of participants reporting AEs through 1 month after vaccination in each vaccine group.

- **The percentage of participants reporting medically attended AEs (MAEs) and serious AEs (SAEs) throughout the study.**

This estimand includes the following 4 attributes:

- Population: Participants who receive 1 dose of investigational product.

- Variable: Presence/absence of the event of interest throughout the study.

- Intercurrent event(s): For participants who discontinue, all collected data will be included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

- Population-level summary: Percentage of participants reporting MAEs and SAEs throughout the study in each vaccine group.

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### 2.2. Study Design

This is a Phase 2b, multicenter, placebo-controlled, randomized, observer-blind study in which approximately 710 healthy nonpregnant women, 18 through 49 years of age, will be randomized to evaluate concomitant administration of the RSV vaccine and a US-licensed tetanus, diphtheria, and acellular pertussis vaccine (Tdap). Participants will be randomized in a 1:1:1:1:1 ratio to receive 1 of the following 5 regimens: 120 µg RSV vaccine antigen (60 µg subgroup A and 60 µg subgroup B) + sterile water for injection (sWFI) with concomitant Tdap, 120 µg RSV vaccine antigen + sWFI with placebo, 240 µg RSV vaccine antigen (120 µg A and 120 µg B) + aluminum hydroxide ($Al[OH]_3$) and concomitant Tdap, 240 µg RSV vaccine antigen + $Al(OH)_3$ and placebo, or placebo and Tdap.

Safety will be assessed through 1 month after vaccination. Immune responses to the RSV vaccine and Tdap antigens will be measured 1 month after vaccination.

Participants will take part in the study from enrollment up to approximately 1 month after vaccination.

## 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

### 3.1. Primary Endpoints

#### 3.1.1. Primary Immunogenicity Endpoints

- Anti–tetanus toxoid and anti–diphtheria toxoid antibodies and antipertussis components (anti-PT, anti-FHA, anti-PRN) measured 1 month after vaccination.
- RSV A– and RSV B–neutralizing antibody titers measured 1 month after vaccination.

#### 3.1.2. Primary Safety Endpoints

- Prespecified local reactions within 7 days after vaccination.
- Prespecified systemic events within 7 days after vaccination.
- AEs from the time of vaccination through 1 month after vaccination.
- MAEs and SAEs throughout the study.

### 3.2. Secondary Endpoints

- RSV A– and RSV B–neutralizing antibody titers measured 1 month after vaccination.

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### 3.4. Baseline Variables

Day 1 is defined as the day of vaccination and the start of the reporting period for local reactions and systemic events in the electronic diary (e-diary).

Day 1 is considered the baseline visit for the following assessments: immunogenicity and vital signs.

### 3.5. Safety Endpoints

#### 3.5.1. Adverse Events

AEs will be captured and reported in accordance with Pfizer reporting standards. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 2.

For participants who are screen failures, the active collection period ends when screen failure status is determined. If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

During the active collection period, both nonserious AEs and SAEs are recorded on the case report form (CRF) and will be categorized according to the current version (at the time of reporting) of the Medical Dictionary for Regulatory Activities (MedDRA).

An immediate AE is defined as any AE that occurs within the first 30 minutes after administration of the investigational product.

An MAE is defined as a nonserious AE that results in an evaluation at a medical facility.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.6.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's Safety Review Plan. There is no preidentified Tier 1 event for this study.

Tier 2 events: These are events that are not Tier 1 but are "common." A MedDRA preferred term is defined as a Tier 2 event if there are at least 4 or more participants in any vaccine group.

Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.



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### 3.5.2. Reactogenicity Data

Reactogenicity data are solicited AEs collected using the e-diary, during Days 1 through 7, starting on the day of vaccination (Day 1). The reactogenicity data will include local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain).

#### 3.5.2.1. Local Reactions

Local reactions reported in the e-diary are redness, swelling, and pain at the injection site.

- **Presence of Local Reactions (Proportion of Participants Reporting)**

The participants will record the presence or absence of pain at the injection site in the e-diary as "Mild," "Moderate," "Severe," or "None." Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21 and 21+) and then categorized as mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following scale: 1 measuring device unit = 0.5 cm. A participant with a severe (Grade 3 or above) local reaction will be prompted to contact the investigator to assess if an unscheduled visit is required to assess the reaction.

**Table 2. Grading Scale for Local Reactions**

| | Mild Grade 1 | Moderate Grade 2 | Severe Grade 3 | Grade 4[a] |
|---|---|---|---|---|
| Redness | >2.0 cm to 5.0 cm (5 to 10 measuring device units) | >5.0 cm to 10.0 cm (11 to 20 measuring device units) | >10 cm (>20 measuring device units) | Necrosis or exfoliative dermatitis |
| Swelling | >2.0 cm to 5.0 cm (5 to 10 measuring device units) | >5.0 cm to 10.0 cm (11 to 20 measuring device units) | >10 cm (>20 measuring device units) | Necrosis |
| Pain (at the injection site) | Does not interfere with activity | Interferes with activity | Prevents daily activity | Emergency room visit or hospitalization for severe pain at the injection site |

a. Only an investigator is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the participant. Grade 4 assessment should only be made by the investigator using the AE severity grading scale. The assessment will be collected on the AE case report form.

Only an investigator is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or, in the case of pain at the injection site only, contact with the participant. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. Grade 4 reactions will be collected on the unscheduled reactogenicity page and as an AE on the CRF. The AE event will be graded using the AE intensity grading scale as indicated in the table "Assessment of Intensity" in Section 10.3.3 of the protocol.

The presence or absence of each local reaction on a given day is defined as follows:

= "Missing," if the value is missing on a given day;

= "Yes," if the participant reports the reaction as "Yes" for redness or swelling (with a diameter of more than 2.0 cm) **or** "Mild," "Moderate," "Severe," or "Grade 4" for pain at the injection site on a given day;

= "No," if the participant reports the reaction as "No" for redness or swelling **or** "None" for pain at the injection site on a given day.

For each local reaction, the derivation of whether or not the specific reaction occurred on "any day (Day 1-7)" will be made. The derivation of this variable is given in Table 3 below.

**Table 3. Derived Variables for Each Local Reaction**

| Variable[a] | Yes (1) | No (0) | Missing (.) |
|---|---|---|---|
| Any day (Day 1-7) | Participant reports the reaction as "Yes" on any day from Day 1 through Day 7. | Participant reports the reaction as "No" on all 7 days or as a combination of "No" and missing on all 7 days. | Participant reports the reaction as missing on all 7 days. |

a. The variable will be defined for each of the 3 local reactions.

For "any local reaction" on any day, a similar definition can be applied, as given in Table 4 below.

**Table 4. Derived Variables for Any Local Reaction**

| Variable | Yes (1) | No (0) | Missing (.) |
|---|---|---|---|
| Any day (Day 1-7) | Participant reports any redness or swelling >2.0 cm or "Yes" for pain at injection site on any day during Days 1 through 7. | Participant reports redness or swelling ≤2.0 cm or pain at injection site as "No" on all 7 days or as a combination of above and missing on all 7 days for all 3 local reactions. | Participant reports all of the local reactions as missing on all 7 days. |

The grading of local reactions is listed above in Table 2.

- **Maximum Severity for Local Reactions**

The maximum severity (highest grading) of each local reaction within 7 days after vaccination will be derived. The maximum severity will be derived as follows:

= "Missing," if values are missing for all days from Days 1 through 7;

= 0, if the participant reports all reactions as "No" or a combination of missing and "No" for all days from Days 1 through 7;

= *highest grade* (maximum severity) within 7 days after vaccination, if the answer is not "No" for at least 1 day.

- **Duration of Each Local Reaction**

The duration of each local reaction will be calculated in days as (resolution date of reaction - start date of reaction + 1). Resolution of the reaction is the last day on which the reaction is recorded in the e-diary or the date the reaction ends if it is unresolved during the participant diary-recording period (end date collected on the CRF), unless chronicity is established. If there is no known end date, the duration will be considered unknown and set to missing.

- **Onset of Local Reaction**

The onset day of each local reaction and any local reaction will be derived.

For the onset day of each local reaction, if participants report severity change for the local reaction, the first day of initial reporting of that specific local reaction will be counted.

For the onset day of any local reaction, the first day of reporting any severity of any local reaction will be counted.

In summary, the following variables will be derived for each local reaction:

1. Presence or absence of each local reaction on each day (Days 1-7) after vaccination.
2. Presence or absence of each local reaction on "any day (Day 1-7)" after vaccination.
3. Presence or absence of any local reaction on "any day (Day 1-7)" after vaccination.
4. Maximum severity of each local reaction on "any day (Day 1-7)" after vaccination.
5. Duration of each local reaction after vaccination.
6. Onset day of each local reaction after vaccination.
7. Onset day of any local reaction after vaccination.

#### 3.5.2.2. Systemic Events

Systemic events reported via the e-diary are fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain. For all ongoing systemic events on Day 7, the stop date will be recorded in the CRF. Additionally, the participant is to document the presence or absence of systemic events in the e-diary as "Mild," "Moderate," "Severe," or "None." Participants will assess the severity of each event according to Table 5.

Only an investigator is able to classify a participant's systemic event as Grade 4, after physical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. A Grade 4 event will be collected on the unscheduled reactogenicity page and as an AE on the CRF. The AE event will be graded using the AE intensity grading scale as indicated in the table "Assessment of Intensity" in Section 10.3.3 of the protocol.

**Table 5. Grading Scale for Systemic Events**

| | Mild Grade 1 | Moderate Grade 2 | Severe Grade 3 | Grade 4[a] |
|---|---|---|---|---|
| Fatigue (= tiredness in diaries) | Does not interfere with activity | Some interference with activity | Prevents daily routine activity | Emergency room visit or hospitalization for severe fatigue |
| Headache | Does not interfere with activity | Some interference with activity | Prevents daily routine activity | Emergency room visit or hospitalization for severe headache |
| Vomiting | 1 to 2 times in 24 hours | >2 times in 24 hours | Requires intravenous hydration | Emergency room visit or hospitalization for severe vomiting |
| Nausea | Does not interfere with activity | Some interference with activity | Prevents daily routine activity | Emergency room visit or hospitalization for severe nausea |
| Diarrhea | 2 to 3 loose stools in 24 hours | 4 to 5 loose stools in 24 hours | 6 or more loose stools in 24 hours | Emergency room visit or hospitalization for severe diarrhea |
| Muscle pain | Does not interfere with activity | Some interference with activity | Prevents daily routine activity | Emergency room visit or hospitalization for severe muscle pain |
| Joint pain | Does not interfere with activity | Some interference with activity | Prevents daily routine activity | Emergency room visit or hospitalization for severe joint pain |

a. Only an investigator is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant or documentation from another medically qualified source (eg, emergency room or hospital record) or contact with the participant. Grade 4 assessment should be made by the investigator using the AE intensity grading scale. The assessment will be collected on the AE case report form.

The highest temperature for each day for 7 days after vaccination is to be recorded in the e-diary. The protocol defines fever as an oral temperature ≥100.4°F (≥38.0°C). Any temperatures recorded as <35.0°C or >42.0°C will be treated as data-entry errors and excluded from the analyses. For reporting purposes, fever will be analyzed using the grading scale in Table 6.

**Table 6. Grading Scale for Fever**

| Mild<br>Grade 1 | Moderate<br>Grade 2 | Severe<br>Grade 3 | Grade 4 |
|---|---|---|---|
| ≥38.0°C to 38.4°C | >38.4°C to 38.9°C | >38.9°C to 40.0°C | >40.0°C |

The presence or absence of each systemic event on a given day is defined as follows:

= "Missing," if the value is missing on a given day;

= "Yes," if the participant reports a temperature ≥38.0°C for fever **or** "Mild," "Moderate," "Severe," or "Grade 4" for the remaining events on a given day;

= "No," if the participant reports a temperature <38.0°C for fever **or** "None" for the remaining events on a given day.

For each systemic event, the following variables will be derived:

1. Presence or absence of each systemic event on each day (Days 1-7) after vaccination.
2. Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
3. Maximum severity of each systemic event on "any day (Day 1-7)" after vaccination.
4. Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.
5. Duration of each systemic event after vaccination.
6. Onset day of each systemic event after vaccination.
7. Onset day of any systemic event after vaccination.

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 3.5.2.1). "Any systemic event" includes any fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain.

### 3.5.3. Laboratory Data

Laboratory assessments will not be collected for this study.

### 3.5.4. Physical Examination, Including Vital Signs

Physical examination will be performed at the screening visit and will include any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes. Height and weight will also be measured and recorded.

Vital signs including sitting systolic and diastolic blood pressure, heart rate, and oral temperature will be measured at the screening visit and recorded in the CRF.

## 4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

| Population | Description |
|---|---|
| Enrolled | All participants who sign the informed consent document. |
| Randomly assigned to investigational product | All participants who are assigned a randomization number in the interactive Web-based response (IWR) system. |
| Evaluable | All participants who:<br>• are eligible;<br>• receive all doses of investigational product to which they were randomized;<br>• have blood drawn for assay testing within the specified time frame (28 to 42 days after vaccination) for 1 month after vaccination;<br>• have at least 1 valid and determinate assay result at the 1-month-postvaccination visit;<br>• and have no major protocol violations.<br>Participants will be analyzed according to the investigational product as randomized. |
| Modified intent-to-treat (mITT) | All randomized participants who receive investigational product and have at least 1 valid and determinate assay result after vaccination.<br>Participants will be analyzed according to the investigational product as randomized. |
| Safety | All randomized participants who receive investigational product. Participants will be analyzed according to the investigational product they actually received. A randomized participant who did not receive investigational product will be excluded from the safety analyses. |

Major protocol violations will be determined by clinical review (through the data handling memo). A major protocol violation is a protocol violation that, in the opinion of the sponsor's study medical monitor, would materially affect assessment of immunogenicity, eg, participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected decrease in potency of the vaccine. The sponsor's medical monitor will identify those participants with protocol violations before any immunogenicity analysis is carried out.

# 5. GENERAL METHODOLOGY AND CONVENTIONS

## 5.1. Hypotheses and Decision Rules

The null hypothesis ($H_0$) for assessing noninferiority with respect to the antipertussis immunogenicity endpoints is:

$$H_0: \ln(\mu_1) - \ln(\mu_2) \leq -\ln(1.5)$$

where $\ln(\mu_1)$ is the mean of the natural logarithm-transformed antibody concentration at 1 month after vaccination from participants in the combined RSV vaccine + Tdap groups, and $\ln(\mu_2)$ is the mean of the natural logarithm-transformed antibody concentration from participants in the placebo + Tdap group. The antibody concentration data will be logarithmically transformed for analysis of GMC ratios along with 95% CIs, and results will be presented on the original scale.

The $H_0$ for assessing noninferiority with respect to the RSV immunogenicity endpoints is:

$$H_0: \ln(\mu_1) - \ln(\mu_3) \leq -\ln(2)$$

where $\ln(\mu_1)$ is the mean of the natural logarithm-transformed antibody titer at 1 month after vaccination from participants in the combined RSV vaccine + Tdap groups, and $\ln(\mu_3)$ is the mean of the natural logarithm-transformed antibody titer from participants in the combined RSV vaccine + placebo groups. The antibody titer data will be logarithmically transformed for analysis of GMT ratios along with 95% CIs, and results will be presented on the original scale.

The $H_0$ for assessing noninferiority with respect to the binary anti–tetanus toxoid and anti-diphtheria toxoid immunogenicity endpoints is:

$$H_0: \pi_1 - \pi_2 \leq -10\%$$

where $\pi_1$ and $\pi_2$ are the percentages of participants with antibody concentrations above certain thresholds at 1 month after vaccination for the combined RSV + Tdap groups and the placebo + Tdap group, respectively.

The noninferiority of RSV vaccine + Tdap to Tdap alone with respect to Tdap immune response will be evaluated at 1 month after vaccination for anti–tetanus toxoid and anti-diphtheria toxoid antibodies and antipertussis components (anti-PT, anti-FHA, and anti-PRN). The primary objective of noninferiority will be met if:

- The lower bound of the 2-sided 95% CI for the difference (combined RSV + Tdap groups minus placebo + Tdap group) in the percentage of participants with anti-tetanus toxoid concentrations ≥0.1 IU/mL is > the predefined limit of -10% (noninferiority margin of 10%); and

- The lower bound of the 2-sided 95% CI for the difference (combined RSV + Tdap groups minus placebo + Tdap group) in the percentage of participants with anti-diphtheria toxoid concentrations ≥0.1 IU/mL is > the predefined limit of -10%; and

- The lower bound of the 2-sided 95% CI for the GMC ratio (combined RSV + Tdap groups divided by placebo + Tdap group) is > the predefined limit of 0.67 (noninferiority margin of 1.5-fold) for each pertussis antigen (PT, FHA, and PRN).

The noninferiority of Tdap + RSV to RSV alone with respect to RSV immune response will be evaluated at 1 month after vaccination for RSV A– and RSV B–neutralizing antibody titers. The primary objective of noninferiority will be met if:

- The lower bounds of the 2-sided 95% CI for the GMT ratio (combined RSV + Tdap groups divided by combined RSV + placebo groups) are > the predefined limit of 0.5 (noninferiority margin of 2-fold) for RSV A– and RSV B–neutralizing antibodies.

The primary hypotheses for Tdap antibody endpoints and the primary hypotheses for RSV A– and RSV B–neutralizing antibody endpoints will be tested simultaneously. The 2 primary objectives of noninferiority will be met only if all statistical criteria for both objectives were met. Therefore, the multiplicity of primary objectives does not require an alpha adjustment.

Conditional upon success of the primary objective for RSV responses, the secondary objective of noninferiority relative to a more stringent margin will be tested. The secondary objective will be met if the lower bounds of the 2-sided 95% CI for the GMT ratio (combined RSV vaccine + Tdap groups divided by combined RSV vaccine + placebo groups) are > the predefined limit of 0.67 (noninferiority margin of 1.5-fold) for RSV A– and RSV B–neutralizing antibodies.

### 5.2. General Methods

Descriptive summary statistics will be provided for all endpoints. Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are the proportion (%) and the n (the numerator) and N (the denominator) used in the calculation of the proportion.

All of the safety, tolerability, and immunogenicity data will be summarized by vaccine group. Immunogenicity results will also be analyzed by combining the RSV vaccine +Tdap groups and/or the RSV vaccine + placebo groups.

#### 5.2.1. Analyses for Binary Endpoints

The number and percentage of participants in each category will be summarized. The 95% CI for percentages, and for difference in percentages, will also be presented, where appropriate.

The 95% CI for the proportion will be constructed by the Clopper-Pearson method described by Newcombe.[1] The 95% CI will be presented in terms of percentages.

The 95% CI for the difference in the proportions will be calculated using the Miettinen and Nurminen method.[2] The 95% CI will be presented in terms of percentages.

#### 5.2.2. Analyses for Continuous Endpoints

Unless otherwise specified, the CI for the mean of a continuous variable will be constructed by the standard method based on Student's t distribution.

##### 5.2.2.1. Geometric Mean Titers (GMTs)

Continuous immunogenicity endpoints will be logarithmically transformed for analysis. GMT and associated 2-sided 95% CI will be calculated at each available time point for each vaccine group. 95% CI will be calculated by back transformation of the 95% CI for the mean of the logarithmically transformed assay results computed using Student's t distribution.

##### 5.2.2.2. Geometric Mean Fold Rise (GMFR)

GMFR will be calculated as the mean difference of an individual participant's logarithmically transformed antibody levels (postvaccination minus baseline) and back transformed to the original units. 95% CI will be computed by back transformation of the 95% CI using Student's t distribution for the mean difference of measures on the logarithmically transformed assay results.

##### 5.2.2.3. Geometric Mean Ratio (GMR)

The GMR will be calculated as the group mean difference of logarithmically transformed antibody levels and back transformed to the original units of the RSV vaccine + Tdap groups to the placebo + Tdap group or to RSV vaccine + placebo groups. Two (2)-sided 95% CI will also be computed by back transformation of the CIs using 2-sample Student's t distribution for the mean difference of measures on the logarithmically transformed assay results.

##### 5.2.2.4. Reverse Cumulative Distribution Curves (RCDCs)

RCDCs for RSV A– and RSV B–neutralizing antibody titers for a combination of available time points and vaccine groups will be generated.

### 5.3. Methods to Manage Missing Data

#### 5.3.1. Safety Data

Standard algorithms on handling missing AE dates and missing AE severity will be applied as described in Pfizer's Vaccine Statistics Rulebook.

##### 5.3.1.1. Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 7-day e-diary is available, the "any day (Day 1-7)" data will be considered nonmissing.

The reactogenicity data are collected through the e-diary, which does not allow participants to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the participant on that day are nonmissing. No missing reactogenicity data will be imputed other than what is described in Section 3.5.2.

### 5.3.2. Immunogenicity Data

For GMT/GMC analysis, a titer reported as < lower limit of quantitation (LLOQ) will be converted to a value of ½ LLOQ. For calculating a fold rise, < LLOQ will be converted to ½ LLOQ for a numerator, and < LLOQ will be converted to LLOQ for a denominator when only one of either the numerator or denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way. For any calculations, a titer reported as > upper limit of quantitation (ULOQ) will be converted to a value of ULOQ.

Values that are designated as serum quantity not sufficient (QNS), designated as indeterminate results, or recorded as "Not Done" will be set to missing. No imputation will be done for these missing values.

## 6. ANALYSES AND SUMMARIES

### 6.1. Primary Endpoints

### 6.1.1. Primary Immunogenicity Endpoints

#### 6.1.1.1. Anti–Tetanus Toxoid and Anti–Diphtheria Toxoid Antibodies and Anti-Pertussis Component (Anti-PT, Anti-FHA, Anti-PRN) Antibody Measured 1 Month After Vaccination

##### 6.1.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Evaluable (Section 4). Participants receiving all doses of investigational products and in compliance with key protocol criteria.
- Analysis methodology: Hypotheses testing.
- Intercurrent events and missing data: All postdiscontinuation or postviolation observations will be censored. Missing results will not be imputed.
- The 95% CIs for the difference (RSV vaccine + Tdap group minus placebo + Tdap group) in the percentage of participants with anti–tetanus toxoid and anti–diphtheria toxoid concentrations ≥0.1 IU/mL will be calculated using the Miettinen and Nurminen method.[2]
- GMRs of the RSV vaccine + Tdap group to the placebo + Tdap group for the anti-PT, anti-FHA, and anti-PRN antibody at 1 month after vaccination will be calculated, along with associated 2-sided 95% CIs.

#### 6.1.1.1.2. Supplementary Analysis

The main analysis will also be performed based on the mITT population. This analysis will be performed only if there is enough difference (eg, ~10%) between the evaluable immunogenicity population and the mITT population.

### 6.1.1.2. RSV A– and RSV B–Neutralizing Antibody Titers Measured at 1 Month After Vaccination

#### 6.1.1.2.1. Main Analysis

- Estimand strategy: Hypothetical.
- Analysis set: Evaluable (Section 4). Participants receiving all doses of investigational products and in compliance with key protocol criteria.
- Analysis methodology: Hypotheses testing.
- Intercurrent events and missing data: All postdiscontinuation or postviolation observations will be censored. Missing results will not be imputed.
- GMRs will be calculated by the ratio of the GMT for RSV A– and RSV B–neutralizing antibody titers from the combined RSV vaccine + Tdap groups to the combined RSV vaccine + placebo group, along with the associated 95% CIs.

#### 6.1.1.2.2. Supplementary Analyses

The main analysis will also be performed based on the mITT population. This analysis will be performed only if there is enough difference (eg, ~10%) between the evaluable immunogenicity population and the mITT population.

### 6.1.2. Primary Safety Endpoints

#### 6.1.2.1. Local Reactions Within 7 Days After Vaccination

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included. Intermediate missing values will not be imputed.
- For each group, n, %, and 95% CI will be presented by vaccine group for the following variables:
    - Presence or absence of each local reaction on each day (Days 1-7) after vaccination.
    - Presence or absence of each local reaction on “any day (Day 1-7)” after vaccination.
    - Presence or absence of any local reaction on “any day (Day 1-7)” after vaccination.

- Maximum severity of each local reaction on "any day (Day 1-7)" after vaccination.

- For each group, n, mean, median, minimum, and maximum will be presented by vaccine group for the following variables:
  - Duration of each local reaction after vaccination.
  - Onset day of each local reaction after vaccination.
  - Onset day of any local reaction after vaccination.

#### 6.1.2.2. Systemic Events Within 7 Days After Vaccination

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics.
- Intercurrent events and missing data: For participants who discontinue, all collected data will be included. Intermediate missing values will not be imputed.
- For each group, n, %, and 95% CI will be presented by vaccine group for the following variables:
  - Presence or absence of systemic event on each day (Days 1-7) after vaccination.
  - Presence or absence of each systemic event on "any day (Day 1-7)" after vaccination.
  - Presence or absence of any systemic event on "any day (Day 1-7)" after vaccination.
  - Maximum severity of each systemic event on "any day (Day 1-7)" after vaccination.
- For each group, n, mean, median, minimum, and maximum will be presented by vaccine group for the following variables:
  - Duration of each systemic event after vaccination.
  - Onset day of each systemic event after vaccination.
  - Onset day of any systemic event after vaccination.

#### 6.1.2.3. AEs Within 1 Month After Vaccination

- Analysis set: Safety (Section 4).
- Analysis methodology: Descriptive summary statistics for Tier 3 events; difference (and 95% CI) between the vaccine group and the placebo group for Tier 2 events.

- Intercurrent events and missing data: For participants who discontinue, all collected data will be included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

- For each group, number of participants with AEs within 1 month (30 days) (n), %, and 95% CI will be presented for any AE, for each system organ class (SOC), and for each preferred term within each SOC, by vaccine group. For AEs classified as Tier 2 events, difference in proportions and associated 2-sided 95% CIs between the vaccine group and the placebo group will be calculated using the Miettinen and Nurminen method.[2]

#### 6.1.2.4. MAEs and SAEs Throughout the Study

- Analysis set: Safety (Section 4).

- Analysis methodology: Descriptive summary statistics.

- Intercurrent events and missing data: For participants who discontinue, all collected data will be included. Missing AE dates will be imputed as described in Pfizer's Vaccine Statistics Rulebook.

- For each group, the numbers of participants with MAEs and SAEs throughout the study (n), %, and 95% CI will be presented for any event, for each SOC, and for each preferred term within each SOC, by vaccine group.

### 6.2. Secondary Endpoints

#### 6.2.1. RSV A– and RSV B–Neutralizing Antibody Titers Measured at 1 Month After Vaccination

The analysis time point and all attributes for this endpoint (including analysis methodology and reporting results) will be similar to those stated in Section 6.1.1.2.1.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

### 6.4. Subset Analyses

Not applicable.

### 6.5. Baseline and Other Summaries and Analyses

#### 6.5.1. Baseline Summaries

For each vaccine group, descriptive summary statistics for demographic characteristics (age at vaccination, sex, race, and ethnicity) will be generated for each vaccine group based on the safety population.

The number and proportion of participants with at least 1 medical history preferred term, arranged by SOC, will be tabulated for each vaccine group. The medical history summary is based on the safety population.

Participant data listings for demography and baseline characteristics data will also be generated.

#### 6.5.2. Study Conduct and Participant Disposition

The number and proportion of randomized participants will be included in the participant disposition summary. In addition, participants who completed the 1-month follow-up visit, and participants who withdrew before the 1-month follow-up visit, along with the reasons for withdrawal, will be tabulated by vaccine group. The reasons for withdrawal will be those as specified in the database.

Participants excluded from the evaluable immunogenicity and mITT populations will also be summarized with reasons for exclusion.

The numbers and proportions of participants who were randomized, were vaccinated, and had blood drawn within the protocol-specified time frames, and outside the specified window, will be tabulated by vaccine group.

The numbers and proportions of participants with e-diary data not transmitted, transmitted by day (Days 1-7), and transmitted on "all days" will be summarized by vaccine group.

Data listings of participants who withdrew during the study will be generated. Also, data listings of participants excluded from the evaluable and mITT populations will be generated separately.

The protocol deviations will be listed. In addition, participants who did not receive the vaccine as randomized will be listed.

### 6.5.3. Concomitant Medications and Nondrug Treatments

Nonstudy vaccines taken after signing the informed consent and until the end of the study will be categorized according to the World Health Organization (WHO) Drug Dictionary and summarized in accordance with the sponsor reporting standards.

## 6.6. Safety Summaries and Analyses

### 6.6.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis. There will be no adjustment for multiple comparison in the analyses.

Analyses and summaries of primary AE endpoints using the 3-tier approach are described in detail in Section 6.1.2.3 and Section 6.1.2.4.

Tier 3 events will be summarized as part of the overall AE summary. Listings of participants reporting any AE and immediate AEs will be generated.

### 6.6.2. Reactogenicity Data

Analysis and summaries of primary reactogenicity endpoints are described in Section 6.1.2.1 and Section 6.1.2.2.

In addition, participant data listings will be provided for all reactogenicity data as well as a listing for participants experiencing severe redness or swelling.

### 6.6.3. Vital Signs

Descriptive summaries (counts and percentages) and listings based on the safety population will be provided in accordance with the Pfizer reporting standards.

## 7. INTERIM ANALYSES

### 7.1. Introduction

No formal interim analysis is planned for this study.

### 7.2. Interim Analyses and Summaries

The final analysis will be performed after all participants completed the study and when all of the data are available.

Additional analysis may include an external data monitoring committee (E-DMC). The E-DMC will review safety data at defined intervals as specified in the charter. The E-DMC may conduct additional meetings to review safety data at other time points during the study, at its discretion, or at the request of the sponsor.

## 8. REFERENCES

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

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26.

# 9. APPENDICES

## Appendix 1. List of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| $Al(OH)_3$ | aluminum hydroxide |
| CI | confidence interval |
| CRF | case report form |
| e-diary | electronic diary |
| E-DMC | external data monitoring committee |
| FHA | filamentous hemagglutinin |
| GMC | geometric mean concentration |
| GMFR | geometric mean fold rise |
| GMR | geometric mean ratio |
| GMT | geometric mean titer |
| $H_0$ | null hypothesis |
| IWR | interactive Web-based response |
| LLOQ | lower limit of quantitation |
| MAE | medically attended adverse event |
| MCAR | missing completely at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent-to-treat |
| N/A | not applicable |
| PRN | pertactin |
| PT | pertussis toxin |
| QNS | quantity not sufficient |
| RCDC | reverse cumulative distribution curve |
| RSV | respiratory syncytial virus |
| RSV A | respiratory syncytial virus subgroup A |
| RSV B | respiratory syncytial virus subgroup B |
| RSV vaccine | respiratory syncytial virus stabilized prefusion F subunit vaccine |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | system organ class |
| sWFI | sterile water for injection |
| Tdap | tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed |
| ULOQ | upper limit of quantitation |
| WHO | World Health Organization |