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

Investigational Product Number:	PF-06928316
Investigational Product Name:	Respiratory Syncytial Virus (RSV) Vaccine
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	C3671004
Phase:	2b

Short Title: A Phase 2b Trial to Evaluate the Safety, Tolerability, and Immunogenicity of a Respiratory Syncytial Virus (RSV) Vaccine When Given Concomitantly With Tetanus, Diphtheria, and Acellular Pertussis Vaccine (Tdap) in Women 18 Through 49 Years of Age

[redacted]

[redacted]

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	21 Jun 2019	Not applicable (N/A)
Protocol Amendment 1	17 Sep 2019	1. Clarification added to each of the formulations of RSV and control vaccines, including Table 1, that will be administered to participants in the study to include the amounts of the active ingredients, adjuvants, and excipients. 2. Clarification added to the criteria for a woman to be considered postmenopausal at the time of study enrollment. 3. Clarification added regarding the use of vital signs (oral temperature, heart rate, and blood pressure) to evaluate participant status prior to investigational product administration and to assist with safety evaluation during an unscheduled reactogenicity visit only. 4. Study sample size increased from approximately 680 participants to approximately 710 participants, because of the addition of a secondary immunogenicity objective recommended by CBER. 5. Secondary immunogenicity objective added as recommended by CBER. Identical to the primary immunogenicity objective, however with noninferiority margins equal to 0.67 and a GMT/GMC ratio of 1 for all antigens to achieve appropriate statistical power. 6. Wording on the possibility of dropping study arms has been removed. 7. Statistics revised (from "2" to "1.5") in the first null hypothesis within Section 9.1. 8. Considerable amount of revisions in the statistical section, including Section 9.2 and Table 5 and Table 6; plus, the addition of Table 7.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Overall Design

This will be 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 a respiratory syncytial virus stabilized prefusion F subunit vaccine (RSV vaccine) and a US-licensed tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap).

Participants will receive 2 injections in accordance with the randomization schedule.

A 0.5-mL dose of RSV vaccine and saline placebo, RSV vaccine and Tdap, or saline placebo and Tdap will be administered intramuscularly by a trial site staff member or designee.

This study will use an external data monitoring committee (E-DMC) to monitor safety in the study.

Number of Participants

Up to approximately 710 participants (Section 9.2) will be randomly assigned to investigational product.

Intervention Groups and Duration

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

Participants will be randomized in a 1:1:1:1:1 ratio to receive one of the following 5 schedules: 120 µg RSV vaccine antigen CCI [redacted] + sterile water for injection (sWFI) with concomitant Tdap, 120 µg RSV vaccine antigen + sWFI with placebo, 240 µg RSV vaccine antigen CCI [redacted] + aluminum hydroxide ($Al[OH]_3$) and concomitant Tdap, 240 µg RSV vaccine antigen + $Al(OH)_3$ and placebo, or placebo and Tdap.

The RSV vaccine lyophilized cake will be reconstituted with diluent using either sWFI for the 120-µg dose level only or a sterile suspension of $Al(OH)_3$ for injection for the 240-µg dose level only. Refer to the investigational product manual (IP manual) for further information.

Table 1. Location of Injection at Visit 1

Formulation	Site of Vaccination
120 µg RSV vaccine + sWFI Placebo	Left deltoid muscle Right deltoid muscle
120 µg RSV vaccine + sWFI Tdap	Left deltoid muscle Right deltoid muscle
240 µg RSV vaccine + $Al(OH)_3$ Placebo	Left deltoid muscle Right deltoid muscle
240 µg RSV vaccine + $Al(OH)_3$ Tdap	Left deltoid muscle Right deltoid muscle
Placebo Tdap	Left deltoid muscle Right deltoid muscle

Abbreviation: sWFI = sterile water for injection.

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.

Medical history, physical examination, and assessment of eligibility will be performed on all participants before randomization. In addition, prespecified local reactions and systemic events will be collected from participants for 7 days after vaccination. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2 and Section 8.2.3.

Discontinuation of study intervention is not applicable in this study. Participants who withdraw after randomization will not be replaced. Dose modification is not applicable in this study. No intervention will be provided to study participants at the end of the study.

Data Monitoring Committee

This study will use an E-DMC to monitor safety in the study (Section 9.5.1).

Statistical Methods

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. A summary of the planned statistical analyses of the primary and secondary endpoints can be found in Section 9.4.

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 (anti-TTd) and anti–diphtheria toxoid (anti-DTd) antibodies and antipertussis components (anti–pertussis toxin [anti-PT], anti–filamentous hemagglutinin [anti-FHA], and antipertactin [anti-PRN]).

The noninferiority of RSV vaccine + Tdap to RSV vaccine alone with respect to respiratory syncytial virus (RSV) immune response will be evaluated at 1 month after vaccination for RSV A– and RSV B–neutralizing antibody titers.

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 are met. Therefore, the multiplicity of primary objectives does not require an alpha adjustment.

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to Section 8 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Number	**1**	**2**
Visit Description	**Day 1 Vaccination**	**Month 1 Follow-up Visit**
Visit Window (Days)		**28 to 35 Days After Visit 1**
Obtain informed consent	X	
Assign participant identifier	X	
Obtain demography and medical history data	X	
Measure weight and height, and calculate BMI	X	
Perform physical examination	X	
Measure vital signs, including oral temperature, seated blood pressure, and heart rate	X	
Perform urine pregnancy test	X	X
Collect and record nonstudy vaccine information	X	X
Review temporary delay criteria	X	
Confirm use of appropriate contraceptives	X	X
Confirm eligibility	X	X
Assign randomization number	X	
Collect blood sample (~50 mL) for antibody assessment	X	X
Administer investigational product	X	
Assess and record acute reactions for at least 30 minutes after investigational product administration	X	
Provide participant with e-diary, thermometer, and measuring device[a]	X	
Online review of e-diary data by the study site (daily review is optimal during the active diary period)	X[b]	
Review and collect e-diary		X
Collect and record AEs, MAEs, and SAEs as appropriate	X → → → → →	X

Abbreviations: BMI = body mass index; e-diary = electronic diary; MAE = medically attended adverse event.

a. Participants will record reactogenicity events each evening for 7 days following vaccination. (Refer to Section 8.10.3 for assessments during unscheduled reactogenicity visits.)
b. Participants will record symptoms in an e-dairy for 7 consecutive days following vaccination.

2. INTRODUCTION

Prevention of RSV disease in young infants is a significant unmet vaccine need globally. RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in very young infants, in infants with underlying cardiopulmonary disease, or in the absence of effective healthcare systems.[1] Worldwide, RSV kills up to 118,200 children annually, with the majority of those deaths occurring in infants under 6 months of age in developing countries.[2,3] In the United States, RSV is the leading cause of infant hospitalization, with more than 60,000 hospitalizations of children 12 months of age and younger annually.[4,5] There is increasing evidence that the link between severe RSV disease in infancy and wheezing later in childhood may be causal.[6] Like influenza, RSV infection follows a seasonal pattern, causing illness primarily in the cooler months of the year in temperate regions and during the wet season in tropical countries with seasonal rainfall,[7] and infection is essentially universal by 2 years of age.[8]

Currently, there is neither specific treatment of RSV infection nor a vaccine to protect against RSV disease. Treatment consists primarily of supportive care. A prophylactic humanized monoclonal antibody, palivizumab (Synagis, AstraZeneca), targeting the RSV fusion (F) glycoprotein is available for prevention of severe RSV disease in young infants at increased risk. Limitations of its use include its high cost[9] and requirement of multiple monthly injections[10] and so it remains recommended for use only in high-risk and very premature infants.[5,11]

Maternal immunization is an increasingly accepted strategy, given the efficacy and safety of aluminum-containing Tdap during pregnancy for mother and baby,[12,13,14] the very good safety record of maternal immunization against influenza during annual seasonal vaccinations, and the increasing evidence of infant benefit from maternal influenza immunization.[15]

There are 2 antigenic variants of RSV, namely, respiratory syncytial virus subgroup A (RSV A) and respiratory syncytial virus subgroup B (RSV B). CCI [redacted]

The RSV vaccine is being developed to prevent RSV-associated lower respiratory tract illness (LRTI) in infants by active immunization of pregnant women.

As it is anticipated that an RSV vaccine may frequently be given with Tdap, this study will assess any impact on immune responses to either vaccine when the RSV vaccine and Tdap are given concomitantly.

2.1. Study Rationale

Pfizer is developing an RSV vaccine for administration to women in the third trimester of pregnancy. Tdap is recommended in the United States and many other countries for administration in the third trimester of pregnancy.[13] Since both vaccines may need to be given in the third trimester to pregnant women, it is important to assess the safety of

[redacted]

concomitant administration and potential for immune interference. This coadministration will be assessed in nonpregnant women where there would be no need to modify the recommended vaccination schedule for pregnant women (eg, delay of Tdap administration) and no potential risk to infant pertussis protection. The study is expected to provide useful data prior to the Phase 3 program in pregnant women and for future practitioners on concomitant use of both vaccines.

2.2. Background

RSV is an important cause of morbidity and mortality worldwide, with a substantial burden of disease borne by young infants. Rates of severe RSV illness are highest in infants <6 months of age, with a peak in hospitalization between 1 and 2 months of life, though the highest case-fatality rates are observed in the neonatal period (<1 month).[16] Infants born prematurely and those with underlying cardiac or pulmonary disease are at further increased risk of severe clinical disease due to RSV. A recent retrospective case analysis that examined RSV mortality data from over 23 countries demonstrates the global nature of the seriousness of RSV disease, with significant morbidity and mortality occurring in both lower- and middle-income country (LMIC) settings, as well as in industrialized nations.[3,4]

No specific treatments for RSV exist, and available prophylactic measures (ie, RSV monoclonal antibody) are limited to use in only those infants at highest risk; additionally, in LMICs, use of available RSV prophylaxis is cost-prohibitive. While active immunization against RSV in infants might be ideal, multiple efforts extending over half a century to develop a safe and effective RSV vaccine to protect infants from disease have yielded little success. The early peak of disease and concerns over vaccine-mediated enhanced RSV respiratory disease present obstacles to an active vaccination strategy for infants. Given these challenges, maternal immunization to protect infants early in life offers an attractive strategy for infant disease prevention.

The present RSV vaccine efforts began in early 2014 based on a new scientific discovery (determination of the prefusion F crystal structure)[17] and a changing regulatory and policy environment that today supports the development of vaccines for maternal immunization to protect very young infants. The trimeric RSV F surface glycoprotein in a prefusion conformation is now known to be the primary target of neutralizing antibodies[18] and is the basis for the engineered antigen in Pfizer's vaccine candidate. Pfizer has used the National Institutes of Health prefusion RSV F crystal structure to guide the development of a stabilized prefusion RSV F vaccine candidate. The core hypothesis underlying Pfizer's RSV vaccine development effort for prevention of infant disease is that vaccine antigen based on prefusion F, when administered to pregnant women in the third trimester of pregnancy, will elicit sufficiently high neutralizing antibody titers to protect against RSV disease via transplacental transfer of antibody to the fetus. Such antibodies would then persist above a given threshold to help protect infants early in life, when they are most at risk for severe RSV disease.

Tdap single dose is recommended for all pregnant women in the United States and many other countries, between 27 and 36 weeks' gestation, although it may be administered at any

time during pregnancy. Tdap may be simultaneously administered with an inactivated influenza vaccine to pregnant women.[13]

2.3. Benefit/Risk Assessment

Pfizer's stabilized prefusion F subunit [redacted] RSV vaccine is being evaluated in ongoing clinical studies. Pfizer's maternal immunization approach circumvents the risk of vaccine-mediated disease enhancement that was observed in the 1960s following direct immunization of RSV-naive infants with a formalin-inactivated RSV vaccine (FI-RSV).[19] FI-RSV elicited a predominantly nonneutralizing antibody response and a Th2-biased cell-mediated response, both of which are considered potential contributing factors to disease enhancement.[20] During preclinical studies, in a standard cotton-rat infectious RSV challenge model, FI-RSV showed pathological signs of causing disease enhancement, whereas the Pfizer vaccine candidate did not (investigational new drug application [IND] Module 2.4). Most important, RSV vaccine-mediated disease enhancement has not been reported to occur in RSV-experienced individuals after immunization with any RSV vaccine candidate. Because adults are universally RSV-experienced, they are not at risk for a disease-enhancing immune response to the vaccine that could exacerbate their infection or their infants. Vaccination with the prefusion RSV F antigen is anticipated to elicit a higher ratio of neutralizing to nonneutralizing antibodies, more closely matching the profile in naturally exposed individuals. The anticipated safety profile of Pfizer's RSV stabilized prefusion F subunit vaccine is expected to be similar to prior postfusion F subunit vaccines tested in RSV-experienced adults.

Diphtheria and tetanus toxoids and acellular pertussis vaccines adsorbed (DTaP) are routinely administered concomitantly with other vaccines in children. Most studies have found that the adverse reactions after multiple simultaneous vaccinations are only slightly greater than would be expected from the most reactogenic vaccine alone.[21,22] Although reduced immunogenicity to the pertussis antigen has occasionally been seen when given in combination or association with 1 or more of the other vaccines, no data exist to suggest that concomitant administration of any of these other vaccines decreases the efficacy of pertussis vaccine.[23,24,25]

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of RSV vaccine may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

The SRSD for the Tdap will be the product information for the United States, where this vaccine will be procured.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Primary Immunogenicity Objectives	Estimands	Primary Immunogenicity Endpoints
To demonstrate that the immune responses induced by Tdap when administered concomitantly with the RSV vaccine (RSV vaccine + Tdap) are noninferior to the immune responses induced by Tdap alone (placebo + Tdap).	In participants receiving at least 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants): • The difference in percentage of participants with anti-TTd antibody concentrations ≥0.1 IU/mL between the combined RSV vaccine + Tdap groups and the placebo + Tdap group. • The difference in percentage of participants with anti-DTd antibody concentrations ≥0.1 IU/mL between the combined RSV vaccine + Tdap groups and the placebo + Tdap group. • Geometric mean concentration (GMC) ratio, estimated by the ratio of the GMC of anti-PT antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group. • GMC ratio, estimated by the ratio of the GMC of anti-FHA antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group. • GMC ratio, estimated by the ratio of the GMC of anti-PRN antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group.	• Anti-TTd and anti-DTd antibodies and antipertussis components (anti-PT, anti-FHA, and anti-PRN) measured 1 month after vaccination.
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).	• Geometric mean titer (GMT) ratio, 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 combined RSV vaccine + placebo groups.	• RSV A– and RSV B–neutralizing antibody titers measured 1 month after vaccination.

Secondary Immunogenicity Objective	Estimand	Secondary Immunogenicity Endpoint
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).	• GMT ratio, 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 combined RSV vaccine + placebo groups.	• RSV A– and RSV B–neutralizing antibody titers measured 1 month after vaccination.
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]		[redacted]
Primary Safety Objective	**Estimands**	**Primary Safety Endpoints**
To evaluate the acceptability of the safety and tolerability profile of the RSV vaccine when administered concomitantly with Tdap and when the RSV vaccine is administered alone.	In participants receiving at least 1 dose of investigational product: • The percentage of participants reporting local reactions. • The percentage of participants reporting systemic events. • The percentage of participants reporting AEs. • The percentage of participants reporting medically attended adverse events (MAEs) and serious adverse events (SAEs).	• Prespecified local reactions within 7 days after vaccination. • Prespecified systemic events within 7 days after vaccination. • AEs within 1 month after vaccination. • MAEs and SAEs throughout the study.

4. STUDY DESIGN

4.1. Overall Design

This will be 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 Tdap. Participants will be randomized in a 1:1:1:1:1 ratio to receive one of the following 5 schedules: 120 µg RSV vaccine antigen CCI [redacted] + sWFI with concomitant Tdap, 120 µg RSV vaccine antigen + sWFI with placebo, 240 µg RSV vaccine antigen CCI [redacted] + $Al(OH)_3$ and concomitant Tdap, 240 µg RSV vaccine antigen + $Al(OH)_3$ and placebo, or placebo and Tdap. Please refer to Table 1.

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.

4.2. Scientific Rationale for Study Design

Refer to Section 2.1.

4.3. Justification for Dose

The doses of vaccine that will be used in this study were determined following assessment of safety and immunogenicity data from the interim analysis of the first-in-human (FIH) study (C3671001).

The FIH study utilized a sentinel cohort (N=168; Phase 1) and an expanded cohort (N=1014; Phase 2). Female and male study participants 18 to 49 years of age and 50 to 85 years of age (sentinel cohort) and 18 to 49 years of age and 65 to 85 years of age (expanded cohort) were enrolled. The FIH study is designed to describe the safety, tolerability, and immunogenicity of up to 6 RSV vaccine candidates CCI [redacted] at 3 escalating dose levels of 60 µg CCI [redacted] 120 µg CCI [redacted] and 240 µg CCI [redacted] of the prefusion RSV F antigen, with or without $Al(OH)_3$, when administered alone or concomitantly with seasonal inactivated influenza vaccine.

An interim analysis of the data from the ongoing FIH study showed a trend toward increasing neutralizing antibody responses for RSV A and RSV B antigens with increasing dose 2 weeks and 1 month after vaccination. The dose response is most apparent when comparing the 120-µg and 240-µg doses, and the highest vaccine responses are generally observed in study participants who received the highest antigen dose. The initial safety data show a benign overall safety profile and no dose response in local reactions, systemic events, or AEs.

RSV dosages in this study encompass the range of doses and formulations that will be used in the planned Phase 3 studies. 120 µg of RSV vaccine without $Al(OH)_3$ is most likely less immunogenic and reactogenic, thus resulting in the lowest immunological interference and least increase of reactogenicity when coadministered with Tdap. 240 µg of RSV vaccine with $Al(OH)_3$ is at the other end of the spectrum, with possible risk of higher reactogenicity and vaccine-to-vaccine immune-response interference when coadministered with Tdap.

4.4. End of Study Definition

A participant is considered to have completed the study if she has completed all phases of the study including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Healthy women ≥18 and ≤49 years of age who are of childbearing potential or not of childbearing potential.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included.

   Note: Female participants who are of childbearing potential and at risk for pregnancy must be willing to use a highly effective method of contraception as outlined in this protocol and for at least 28 days after the last dose of investigational product. Refer to Appendix 4 (Section 10.4) for reproductive criteria for female participants.

Type of Participant and Disease Characteristics:

2. Willing and able to comply with all scheduled visits, treatment plan, lifestyle considerations, and other study procedures.

3. Expected to be available for the duration of the study and can be contacted by telephone during study participation.

Weight:

4. Body mass index (BMI) of <40 kg/m^2 at the time of the consent.

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the vaccines being administered in the study.

4. History of latex allergy.

5. Immunocompromised participants with known or suspected immunodeficiency, as determined by history, laboratory tests, and/or physical examination.

6. Any contraindication to Tdap (including encephalopathies).

7. History of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

8. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

9. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

10. Previous vaccination with any licensed or investigational RSV vaccine, or planned receipt of nonstudy RSV vaccine throughout the study.

11. Treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until

corticosteroid therapy has been discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

12. Receipt of blood/plasma products or immunoglobulin within 60 days before investigational product administration or planned receipt throughout the study.

13. Current alcohol abuse, marijuana abuse, or illicit drug use.

14. Vaccination within 5 years with DTaP or tetanus and diphtheria toxoids adsorbed (Td) vaccine before investigational product administration.

Prior/Concurrent Clinical Study Experience:

15. Participation in other studies involving investigational drug(s), investigational vaccine(s), or investigational device(s) within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

Diagnostic Assessments:

Not applicable.

Other Exclusions:

16. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.2.1. Criteria for Temporarily Delaying Vaccine Administration

The following conditions are temporary or self-limiting, and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (oral temperature ≥38.0°C [≥100.4°F]) or other acute illness within 48 hours before investigational product administration.

2. Receipt of any inactivated vaccine within 14 days and any live vaccine within 28 days before or anticipated receipt of any vaccine within the 14 days after investigational product administration.

3. Receipt of short-term (<14 days) systemic corticosteroids. Investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids do not require temporary delay of investigational product administration.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and her partner(s) from the permitted list of contraception methods (see Appendix 4 [Section 10.4]) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to investigational product. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

For this study, the investigational product(s) are RSV vaccine, Tdap, and placebo (saline control). US-licensed Tdap will be provided by the sponsor.

6.1.1. Respiratory Syncytial Virus Stabilized Prefusion F Subunit Vaccine

Each lyophilized vial of the RSV vaccine drug product will be supplied as [redacted] a lyophilized cake.

[redacted]

CCI [redacted]

The fill volume of the drug product vial and diluent vial are designed such that the intended vaccine dose is delivered in a 0.5-mL injection volume. The stopper of the sWFI vial may contain natural rubber latex. Refer to the IP manual for further information.

6.1.2. Placebo

The placebo for the RSV vaccines and Tdap will be a sterile normal saline solution for injection (0.9% NaCl injection, in a 0.5-mL dose).

Placebo will be provided by the sponsor to each study site.

Placebo will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements.

6.1.3. Tetanus, Diphtheria, and Acellular Pertussis Vaccine (Tdap)

US-licensed Tdap will be provided by the sponsor to each study site.

Investigational sites will be provided with details of which US-licensed Tdap will be provided prior to the start of enrollment. The active ingredients of Tdap will contain the following (per dose): 5 Lf (limits of flocculation) of TTd, 2.5 Lf of DTd, acellular pertussis antigens (8 µg of inactivated PT, 8 µg of FHA, and 2.5 µg of PRN).

The Tdap will also contain the following excipient concentrations: <0.39 mg $Al(OH)_3$, 4.4 mg NaCl, ≤100 µg of residual formaldehyde, and ≤100 µg of polysorbate 80.

Note: The stopper of the Tdap vial may contain natural rubber latex.

6.1.4. Administration

Participants will receive 2 injections (see Table 1) at Visit 1 in accordance with the randomization schedule.

A 0.5-mL dose of RSV vaccine and saline placebo, RSV vaccine and Tdap, or saline placebo and Tdap will be administered intramuscularly by an unblinded site staff member or designee.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute

[redacted]

hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of investigational products should be performed by an appropriately qualified, Good Clinical Practice (GCP)-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Investigational product administration details will be recorded on the case report form (CRF).

Additional information for this compound may be found in the SRSD, which for this study is the IB. The SRSD for the Tdap will be the product information for the United States, where the vaccine was procured.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

- Only participants enrolled in the study may receive study intervention and only authorized site staff may administer study intervention.

- All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

- Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

- Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

- Study interventions should be stored in their original containers and in accordance with the labels.

- See the IP manual for storage conditions of the study intervention once reconstituted.

- Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

- The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

Refer to the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Investigational product and placebo will be prepared and administered by qualified unblinded site personnel according to the IP manual. The investigational product will be administered to blinded participants.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Blinding of Study Site Personnel

This is an observer-blinded study as the physical appearance of the RSV vaccine, Tdap, and placebo may differ.

The participant, investigator, study coordinator, and other site staff will be blinded. At the study site only the dispenser(s)/administrator(s) are unblinded.

Contact between the unblinded dispenser(s)/administrator(s) and participants should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispenser(s)/administrator(s) must not be allowed to know the investigational

product assigned to any participant and must not be allowed to see the investigational product.

6.3.2. Blinding of the Sponsor

The sponsor study team members will be blinded until the database is locked and unblinded; see Section 9.5.1.

Laboratory personnel performing the serology assays will remain blinded to vaccine assigned/received throughout the study.

Those study team members who are involved in ensuring that protocol requirements for investigational product handling, allocation, and administration are fulfilled at the site (eg, study manager; clinical research associates) will be unblinded for the duration of the study.

6.3.3. Allocation to Investigational Product

Participants will be assigned to receive investigational product according to randomization scheme. Allocation of participants to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]).

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded investigational product records at the site(s) to verify that randomization/dispensing has been done accurately.

6.3.4. Breaking the Blind

At the initiation of the study, the investigator will be instructed on the method for breaking the blind for an individual participant. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

6.5. Concomitant Therapy

6.5.1. Prohibited Nonstudy Vaccines Prior to the Study

- Receipt of any licensed or investigational RSV vaccine(s) at any time.

- Receipt of any inactivated vaccine within 14 days or any live vaccine within 28 days before investigational product administration.

- Vaccination within 5 years with DTaP or Td vaccine before investigational product administration.

6.5.2. Prohibited Nonstudy Vaccines and Medications During the Study

- Nonstudy investigational vaccines, investigational drugs, or investigational medical devices are prohibited during the study.

- Licensed or investigational RSV vaccines and blood/plasma products or immunoglobulins are prohibited during the study.

- Systemic immunosuppressive therapy is prohibited during the study.

- Unless considered medically necessary, no vaccines should be administered until at least 14 days after investigational product administration.

- Prophylactic antipyretics and other pain medication to prevent symptoms associated with investigational product administration are not permitted.

6.5.3. Permitted Nonstudy Vaccines and Medications During the Study

- If medically necessary (eg, pandemic or outbreak with pandemic potential), influenza vaccine may be given at any time.

- The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration is permitted during the study.

- Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

- Medications and treatments other than those described as prohibited are permitted.

6.5.4. Recording Nonstudy Vaccinations

The name and date of administration for any nonstudy vaccination(s) received from the time of signing of the ICD until the final visit will be collected and recorded in the CRF.

6.6. Dose Modification

Dose modification is not applicable in this study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Discontinuation of study intervention is not applicable in this study.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Participants who withdraw after randomization will not be replaced.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1 (Section 10.1).

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Safety parameters will be assessed as described in the SoA and below.

Medical history, physical examination, and assessment of eligibility will be performed on all participants before randomization. In addition, prespecified local reactions and systemic events will be collected from participants for 7 days after vaccination. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 8.2.2 and Section 8.2.3.

Significant medical history and observations from the physical examination will be documented in the CRF. In addition, AEs, MAEs, and SAEs are collected, recorded, and reported as defined in Section 8.3 and Section 10.3.3. An MAE is defined as a nonserious AE that results in an evaluation at a medical facility.

8.2.1. Electronic Diary

The participant will be asked to monitor and record local reactions, systemic events, and temperature each evening for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination). The electronic diary (e-diary) allows recording of these assessments only within a fixed time window each day, thus providing the accurate representation of the participant's experience at that time.

Data on local reactions, systemic events, and temperatures recorded on the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators, their qualified designees, and sponsor staff at all times via an internet-based portal. At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically to Pfizer for analysis and reporting. These data do not need to be recorded by the investigator in the CRF. However, if a participant withdraws because of prompted events recorded in the e-diary, the event(s) should be recorded on the AE page of the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

Investigators (or appropriately qualified designees) are required to review the e-diary data online to evaluate participant compliance and as part of the ongoing safety review.

The investigator or designee must obtain stop dates for any reactions ongoing on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2. Local Reactions

Following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), participants will be asked to assess redness, swelling, and pain at the injection site of the left arm and to record the symptoms in the e-diary in the evening.

Redness and swelling of the injection site on the left arm will be measured and recorded in measuring device units (range: 1 to 21 and 21+) and then categorized during analysis 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 severe redness, swelling, or pain at the injection site will be prompted to contact the investigator to assess if an unscheduled visit is required to assess the reaction. In addition, if a participant experiences necrosis of the left arm or exfoliative dermatitis, she should contact the investigator to assess if an unscheduled visit is required to assess the reaction.

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 of the left arm 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 as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Site staff will educate the participant regarding signs and symptoms (including necrosis at the injection site of the left arm or exfoliative dermatitis) that would prompt site contact. The procedure for notification of the sponsor is provided in the study documentation.

If a local reaction persists beyond the end of the e-diary period, the participant will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the participant's source notes and CRF.

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

Table 2. Grading Scale for Local Reactions

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
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 of the left arm only, 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.

8.2.3. Systemic Events

Following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination), participants will be asked to assess fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain and to record the symptoms in the e-diary in the evening. The symptoms will be assessed by the participant according to the grading scale in Table 3 below. Study staff may also contact the participant to obtain additional information on events entered into the e-diary.

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. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. The procedure for notification of the sponsor is provided in the study documentation. Grade 4 reactions will be collected as an AE on the CRF. The event will be graded using the AE intensity grading scale (Section 10.3.3).

Further, if a systemic event persists beyond the end of the e-diary period, the participant will be requested to report that information and/or any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Table 3. 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

Table 3. Grading Scale for Systemic Events

	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Grade 4[a]
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 event will be collected on the AE case report form.

8.2.4. Fever

A digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected in the evening daily for 7 days following vaccination (Day 1 through Day 7, where Day 1 is the day of vaccination) and at any time during the 7 days following vaccination that fever is suspected. Fever is defined as an oral temperature of ≥38.0°C (≥100.4°F). The highest temperature for each day will be recorded in the e-diary.

In the event of a fever on Day 7, temperature will be measured daily until fever has resolved (1 day of temperature less than 38.0°C [100.4°F]) in order to collect a stop date in the CRF.

A participant with a fever >38.9°C (>102°F) will be prompted to contact the investigator. The investigator or designee will assess the fever and perform an unscheduled visit as appropriate.

Temperature will be measured and recorded to 1 decimal place and then grouped into ranges for the analysis according to Table 4 below. Temperatures reported in degrees Fahrenheit will be programmatically converted to degrees Celsius for reporting.

Table 4. Ranges for Fever

Fever	≥38.0°C to 38.4°C	>38.4°C to 38.9°C	>38.9°C to 40.0°C	>40.0°C

8.2.5. Physical Examinations

The physical examination 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.

8.2.6. Vital Signs

Oral temperature, seated blood pressure, and heart rate will be measured.

The vital signs will be used to evaluate participant status prior to investigational product administration and to assist with safety evaluation during an unscheduled reactogenicity visit. These data are to assist the investigator with participant evaluation during the study.

- Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.7. Clinical Safety Laboratory Assessments

Laboratory assessments will not be collected for this study.

8.2.8. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2.9. RSV Vaccine Antibody Testing

Sera collected will be assayed for RSV A– and RSV B–neutralizing antibody levels, and may be assayed for anti-RSV prefusion F immunoglobulin G (IgG) levels, and immunoglobulin (Ig) levels against nonvaccine RSV antigens.

RSV A– and RSV B–neutralizing antibody levels will be determined and reported as the neutralizing titer. IgG levels will be determined against [redacted] prefusion F antigen [redacted] in a direct-binding Luminex immunoassay (dLIA) and reported as an anti–prefusion F IgG titer (units/mL). Ig levels against nonvaccine RSV antigens may also be tested by dLIA.

Additional, exploratory tests of immunity against RSV nonvaccine antigens and against RSV vaccine antigens may also be performed.

Testing will be performed by Pfizer and/or a facility designated by Pfizer.

8.2.10. Tdap Antibody Testing

Sera collected will be assayed for IgG antibodies to Tdap antigens in a multiplexed Luminex bead-based assay: DTP-6 IgG. IgG levels to DTd, TTd, and pertussis antigens (PT, PRN, and FHA) will be measured and reported in either IU/mL (DTd and TTd) or EU/mL (PT, FHA, and PRN).

Testing will be performed by Pfizer and/or a facility designated by Pfizer.

[redacted]

8.2.12. Total Volume of Blood Collected

The total volume of blood collected for antibody assessment will be up to approximately 100 mL (~50 mL/visit) over the course of the study.

8.2.13. Pregnancy Testing

Urine pregnancy tests must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in women of childbearing potential (WOCBP) at the times listed in the SoA. A negative pregnancy test will be required at Visit 1 prior the participant's receiving the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by

[redacted]

institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3 (Section 10.3).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue from the study (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

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.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this

exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until 28 days after the vaccination.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 Section 10.4. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Other examples include, but are not limited to:

- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;
- The administration by an incorrect route,
- The administration of investigational product that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the investigational product under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 0.5 mL will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant.
3. Document the quantity of the excess dose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

No interruptions or dose modifications will be made in this study.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.10. Procedures

8.10.1. Visit 1: Vaccination (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Assign single participant identifier using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Measure vital signs, including oral temperature, seated blood pressure, and heart rate.
- Measure and record weight and height.
- Calculate BMI.
- Perform physical examination evaluating 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.
- Prior to vaccination, perform a urine pregnancy test for female participants of childbearing potential.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Collect and record nonstudy vaccinations as described in the SoA (Section 1.3) and Section 6.5.4.
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.2.1.
- Confirm understanding of and compliance with protocol requirements for contraception.
- Obtain the participant's randomization number and investigational product kit number using the IRT system. Either blinded site staff or unblinded site staff member may obtain this information.
- Prior to vaccination, collect a blood sample of approximately 50 mL for antibody assessment.
- Unblinded site staff member(s) will dispense/administer a 0.5-mL injection of investigational product into the deltoid muscle of the left arm and a 0.5-mL injection of

investigational product into the deltoid muscle of the right arm (see Section 6.1.4). Please refer to the IP manual for further instruction on this process.

- Blinded site staff must observe the participant for any acute reactions for at least 30 minutes after investigational product administration.
- Assess and record any acute reactions in the participant's source documents, on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site of the left arm and a digital thermometer for recording daily temperatures, and provide instructions on their use.
- Issue the participant an e-diary and provide instructions on its completion. Ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
  - Fever ≥39.0°C (≥102.1°F).
  - Redness or swelling at the injection site on the left arm measuring >10 cm (>20 measuring device units).
  - Severe pain at the injection site on the left arm.
  - Any blackening of the skin (necrosis) at the injection site on the left arm.
  - Any peeling/scaling of the skin (exfoliative dermatitis).
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Remind participants that study staff may contact them to obtain additional information on events entered into the e-diary.
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the completed e-diary to the next visit.
- Collect and record AEs (including MAEs) and SAEs, as described in Section 8.3.1.
- Complete the source documents.

- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the investigational product accountability records.

- The investigator or appropriately qualified designee reviews the e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period, up to Day 7 following study vaccination.

8.10.2. Visit 2: 1-Month Follow-up Visit (28-35 Days After Visit 1)

- Review the participant's e-diary data and collect the e-diary. Collect stop dates of any e-diary events ongoing on the last day that the e-diary was completed and record stop dates in the CRF if required.

- Confirm understanding of and compliance with protocol requirements for contraception.

- Perform a urine pregnancy test for female participants of childbearing potential.

- Ensure and document that the participant is still eligible for the study.

- Collect a blood sample of approximately 50 mL for antibody assessment.

- Collect and record nonstudy vaccinations as described in Section 6.5.4.

- Collect and record AEs (including MAEs) and SAEs, as described in Section 8.3.1.

- Complete the source documents.

- The investigator or an authorized designee completes the CRFs.

8.10.3. Unscheduled Reactogenicity Visits

If the participant reports 1 or more of the following, a contact **must** occur as soon as possible between the participant and the investigator, or a medically qualified member of the study site staff, to assess if an unscheduled visit is required.

- redness at the injection site on the left arm measuring >20 measuring device units (>10.0 cm),

- swelling at the injection site on the left arm measuring >20 measuring device units (>10.0 cm),

- severe injection site pain on the left arm,

- fever ≥39.0°C (≥102.1°F).

A site visit should be scheduled as soon as possible to assess the extent of the reaction unless:

- The participant is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the contact, or
- The participant recorded an incorrect value in the e-diary (confirmation of an e-diary data entry error), or
- The investigator determines that the visit is not required.

This contact will be recorded in the participant's source notes and in the CRF.

If the participant is unable to attend the unscheduled visit, any ongoing reactions must be assessed at the next scheduled visit.

The reactogenicity events should be assessed by the investigator or a medically qualified member of the site staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure oral temperature.
- Measure the participant's heart rate.
- Measure the participant's blood pressure (seated).
- Measure the minimum and maximum diameters of redness on the left arm (if present).
- Measure the minimum and maximum diameters of swelling on the left arm (if present).
- Assess any necrosis at the injection site on the left arm.
- Assess any exfoliative dermatitis.
- Assess any injection site pain on the left arm that is present in accordance with the reactogenicity grading scale provided in Section 8.2.2.
- Assess any systemic events (fatigue, headache, nausea, vomiting, diarrhea, muscle pain, or joint pain) that are present in accordance with the reactogenicity grading scale provided in Section 8.2.3.
- Ask the participant if she attended an emergency room visit or was hospitalized.
- For severe pain at the injection site on the left arm associated with an emergency room visit or hospitalization, severe systemic events associated with an emergency room visit or hospitalization, or any necrosis on the left arm or exfoliative dermatitis, the

investigator must assess these events in accordance with the intensity AE grading scale provided in Section 8.2.2 and Section 8.2.3 for documentation on the AE CRF.

- Collect and record AEs (including MAEs) and SAEs as described in Section 8.3.1 and complete the source documents.

- The investigator or an authorized designee will complete the CRFs.

Participants will be instructed to contact the site to report any significant illness, medically attended event, or hospitalization that occurs during the study period. Study staff may contact the participant to obtain additional information on Grade 3 events entered into the e-diary.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

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% confidence intervals (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 for binary antidiphtheria and antitetanus immunogenicity endpoints is:

H_0: $\pi 1 - \pi 2 \leq -10\%$

where π_1 and π_2 are the percentages of participants with antibody concentrations above certain thresholds at 1 month after vaccination for the combined RSV vaccine + 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-TTd and anti-DTd 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 vaccine + Tdap groups minus placebo + Tdap group) in the percentage of participants with antitetanus 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 vaccine + Tdap groups minus placebo + Tdap group) in the percentage of participants with antidiphtheria 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 vaccine + 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 RSV vaccine + Tdap to RSV vaccine 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 vaccine + Tdap groups divided by combined RSV vaccine + 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 are 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.

9.1.1. Estimands

Immunogenicity:

In participants receiving at least 1 dose of investigational product and in compliance with the key protocol criteria (evaluable participants):

- The difference in percentage of participants with anti-TTd antibody concentrations ≥0.1 IU/mL between the combined RSV vaccine + Tdap groups and the placebo + Tdap group
- The difference in percentage of participants with anti-DTd antibody concentrations ≥0.1 IU/mL between the combined RSV vaccine + Tdap groups and the placebo + Tdap group
- GMC ratio, estimated by the ratio of the GMC of anti-PT antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group
- GMC ratio, estimated by the ratio of the GMC of anti-FHA antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group
- GMC ratio, estimated by the ratio of the GMC of anti-PRN antibodies from the combined RSV vaccine + Tdap groups to the placebo + Tdap group
- GMT ratio, 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 combined RSV vaccine + placebo groups.

These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing serology results will not be imputed, as missing completely at random (MCAR) is assumed. For participants who discontinue from the study or have major protocol violations, all postdiscontinuation or violation observations will be censored.

Safety:

In participants receiving at least 1 dose of investigational product:

- The percentage of participants reporting local reactions.
- The percentage of participants reporting systemic events.
- The percentage of participants reporting AEs.

- The percentage of participants reporting MAEs and SAEs.

Missing e-diary data will not be imputed; missing AE dates and missing AE severity will be handled according to Pfizer safety rules.

9.2. Sample Size Determination

The study has 2 primary immunogenicity objectives. The study sample size is based upon the evaluation of noninferiority of RSV vaccine coadministration with Tdap to Tdap alone or to RSV vaccine alone on 7 coprimary endpoints. For the continuous immunogenicity endpoints, ie, GMC/GMT ratio, noninferiority will be evaluated using a 2-fold margin as the criterion for RSV endpoints, and a 1.5-fold margin as the criterion for pertussis endpoints. A 10% margin will be used to evaluate noninferiority for the binary immunogenicity endpoints. It was assumed that there was no inherent difference between the 2 groups (ie, a GMC/GMT ratio of 1 for the continuous endpoints and a difference of 0% for the binary endpoints).

Table 5 presents the power to demonstrate noninferiority, for the 2 RSV vaccine formulations combined. The power calculations were performed using PROC POWER in SAS 9.4. With 128 evaluable participants in each group, the study will have 92.2% power to demonstrate noninferiority of the combined RSV vaccine formulations coadministered with Tdap to Tdap alone with respect to GMC of antipertussis components (anti-PT, anti-FHA, and anti-PRN), and have >99.9% power to demonstrate noninferiority of the combined RSV vaccine formulations coadministered with Tdap to RSV vaccine alone with respect to GMT of RSV A– and RSV B–neutralizing antibody titers. The study will also have 99.9% power to demonstrate noninferiority of the combined RSV vaccine formulations coadministered with Tdap to Tdap alone with respect to the percentage of participants with antitetanus and antidiphtheria antibody concentrations ≥0.1 IU/mL. The overall power to demonstrate noninferiority on all 7 primary endpoints is 92.1%.

Assuming a nonevaluable rate of 10%, the study will randomize up to approximately 710 participants to achieve 128 evaluable participants in each group.

Table 5. Power to Show Noninferiority of Combined RSV Vaccine Formulations Administered With Tdap (RSV + Tdap) to Tdap Alone (Placebo + Tdap) and RSV Vaccine Alone

Endpoint	% in Placebo + Tdap Group[a]	Assumed % in RSV + Tdap Group	NI Margin[b]	N Evaluable/Group		Power[c]
				Placebo + Tdap	RSV + Tdap	
Anti-TTd	97.4%	97.4%	10%	128	256	99.9%
Anti-DTd	98.3%	98.3%	10%	128	256	>99.9%
Power to show NI for both anti-TTd and anti-DTd						**99.9%**

Table 5. Power to Show Noninferiority of Combined RSV Vaccine Formulations Administered With Tdap (RSV + Tdap) to Tdap Alone (Placebo + Tdap) and RSV Vaccine Alone

Endpoint	Standard Deviation (ln)[a]	Assumed GMC Ratio	NI Margin[d]	N Evaluable/Group		Power[c]
				Placebo + Tdap	RSV + Tdap	
Anti-PT	0.967	1	1.5-fold	128	256	97.2%
Anti-FHA	0.737	1	1.5-fold	128	256	99.8%
Anti-PRN	1.036	1	1.5-fold	128	256	95.0%
Power to show NI for anti-PT, anti-FHA, and anti-PRN						**92.2%**
Endpoint	**Standard Deviation (ln)[a]**	**Assumed GMC Ratio**	**NI Margin[e]**	**N Evaluable/Group**		**Power[c]**
				RSV + Placebo	**RSV + Tdap**	
RSV A	1.002	1	2-fold	256	256	>99.9%
RSV B	1.087	1	2-fold	256	256	>99.9%
Power to show NI for both RSV A and RSV B						**>99.9%**
Power to show NI for all 7 primary endpoints						**92.1%**

Abbreviations: anti-DTd = anti–diphtheria toxoid; anti-TTd = anti–tetanus toxoid; FHA = filamentous hemagglutinin; GMC = geometric mean concentration; NI = noninferiority; PRN = pertactin; PT = pertussis toxin.

a. Reference study B1971015 (Tdap endpoints); C3671001 sentinel cohort (RSV vaccine endpoints).
b. NI met if lower limit of 95% CI for the difference (RSV+Tdap – placebo+Tdap) > -10%.
c. At 0.05 alpha level (2-sided).
d. NI met if lower limit of 95% CI for the GMC ratio [(RSV+Tdap)/(placebo+Tdap)] > 0.67.
e. NI met if lower limit of 95% CI for the GMT ratio [(RSV+Tdap)/(RSV+placebo)] > 0.5.

For the sample size of 710 randomized participants, Table 6 presents the power to demonstrate noninferiority for an individual RSV vaccine formulation. The power calculations were performed using PROC POWER in SAS 9.4. With 128 evaluable participants in each group, the study will have 79.3% power to demonstrate noninferiority of an individual RSV vaccine formulation coadministered with Tdap to Tdap alone with respect to the GMC of antipertussis components (anti-PT, anti-FHA, and anti-PRN), and have 99.9% power to demonstrate noninferiority of an individual RSV vaccine formulation coadministered with Tdap to RSV vaccine alone with respect to the GMT of RSV A– and RSV B–neutralizing antibody titers. The study will also have 97.8% power to demonstrate noninferiority of an individual RSV vaccine formulation coadministered with Tdap to Tdap alone with respect to the percentage of participants with antitetanus and antidiphtheria antibody concentrations ≥0.1 IU/mL. The overall power to demonstrate noninferiority on all 7 primary endpoints is 77.5%.

Table 6. Power to Show Noninferiority of Individual RSV Vaccine Formulations Administered With Tdap (RSV + Tdap) to Tdap Alone (Placebo + Tdap) and RSV Vaccine Alone

Endpoint	% in Placebo + Tdap Group[a]	Assumed % in RSV + Tdap Group	NI Margin[b]	N Evaluable/Group		Power[c]
				Placebo + Tdap	RSV + Tdap	
Anti-TTd	97.4%	97.4%	10%	128	128	98.1%
Anti-DTd	98.3%	98.3%	10%	128	128	99.7%
Power to show NI for both anti-TTd and anti-DTd						**97.8%**
Endpoint	**Standard Deviation (ln)[a]**	**Assumed GMC Ratio**	**NI Margin[d]**	**N Evaluable/Group**		**Power[c]**
				Placebo + Tdap	**RSV + Tdap**	
Anti-PT	0.967	1	1.5-fold	128	128	91.7%
Anti-FHA	0.737	1	1.5-fold	128	128	98.5%
Anti-PRN	1.036	1	1.5-fold	128	128	87.8%
Power to show NI for anti-PT, anti-FHA, and anti-PRN						**79.3%**
Endpoint	**Standard Deviation (ln)[a]**	**Assumed GMC Ratio**	**NI Margin[e]**	**N Evaluable/Group**		**Power[c]**
				RSV + Placebo	**RSV + Tdap**	
RSV A	1.002	1	2-fold	128	128	>99.9%
RSV B	1.087	1	2-fold	128	128	99.9%
Power to show NI for both RSV A and RSV B						**99.9%**
Power to show NI for all 7 primary endpoints						**77.5%**

Abbreviations: anti-DTd = anti–diphtheria toxoid; anti-TTd = anti–tetanus toxoid; FHA = filamentous hemagglutinin; GMC = geometric mean concentration; GMT = geometric mean titer; NI = noninferiority; PRN = pertactin; PT = pertussis toxin.

a. Reference study B1971015 (Tdap endpoints); C3671001 sentinel cohort (RSV vaccine endpoints).
b. NI met if lower limit of 95% CI for the difference (RSV+Tdap – placebo+Tdap) > -10%.
c. At 0.05 alpha level (2-sided).
d. NI met if lower limit of 95% CI for the GMC ratio [(RSV+Tdap)/(placebo+Tdap)] > 0.67.
e. NI met if lower limit of 95% CI for the GMT ratio [(RSV+Tdap)/(RSV+placebo)] > 0.5.

The sample size of 710 also allows for at least 90% overall power, if the noninferiority margin of 1.5 applies to the RSV responses, as in the secondary objective. Table 7 summarizes the power for the secondary objective and the power for the overall test of noninferiority including the 1.5-fold margin for the RSV responses.

Table 7. Power to Show Noninferiority of Combined RSV Vaccine Formulations Administered With Tdap (RSV + Tdap) to Tdap Alone (Placebo + Tdap) and RSV Vaccine Alone, Using 1.5-Fold Margin for RSV Responses

Endpoint	Standard Deviation (ln)[a]	Assumed GMC Ratio	NI Margin[b]	N Evaluable/Group		Power[c]
				RSV + Placebo	RSV + Tdap	
RSV A	1.002	1	1.5-fold	256	256	99.5%
RSV B	1.087	1	1.5-fold	256	256	98.8%
Power to show NI for both RSV A and RSV B						**98.3%**
Power to show NI for RSV responses and all Tdap responses (per primary endpoints)						**90.5%**

Abbreviations: GMC = geometric mean concentration; GMT = geometric mean titer; NI = noninferiority.
a. Reference study C3671001 sentinel cohort.
b. NI met if lower limit of 95% CI for the GMT ratio [(RSV+Tdap)/(RSV+placebo)] > 0.67.
c. At 0.05 alpha level (2-sided).

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants who are assigned a randomization number in the IWR system.
Evaluable	All participants who are eligible, receive all doses of the investigational products to which they were randomized, have blood drawn for assay testing within the specified time frame for 1 month after vaccination, have at least 1 valid and determinate assay result at the 1 month postvaccination visit, and have no major protocol violations.
Modified intent-to-treat (mITT)	All randomized participants who receive at least 1 dose of the investigational product and have at least 1 valid and determinate assay result after vaccination.
Safety	All randomized participants who receive at least 1 dose of the investigational product.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Primary	• The 95% CIs for the difference (RSV vaccine + Tdap group minus placebo + Tdap group) in the percentage of participants with antitetanus and antidiphtheria concentrations ≥0.1 IU/mL will be calculated using the Miettinen and Nurminen method.

Endpoint	Statistical Analysis Methods
	• Geometric mean ratios (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. The GMR will be calculated as the group mean difference of logarithmically transformed antibody levels and transformed back to the original units. Two (2)-sided 95% CIs will also be obtained by calculating CIs using a 2-sample Student's t distribution for the mean difference of measures on the logarithmically transformed assay results, and transforming confidence limits back to the original units. • GMRs of the RSV vaccine + Tdap group to the RSV vaccine + placebo group for the RSV A– and RSV B–neutralizing antibody titers at 1 month after vaccination will be calculated, along with associated 2-sided 95% CIs, using the same method as for anti-PT, anti-FHA, and anti-PRN antibody GMRs. Titers below the lower limit of quantitation (LLOQ) or denoted as below the limit of quantitation (BLQ) will be set to 0.5 × LLOQ for GMT/GMC analysis. This analysis is based on the evaluable population in order to provide a comparison of the 2 groups that has the greatest chance of identifying a difference between the groups with respect to immunogenicity, if a meaningful difference actually exists (ie, results of the comparisons fail to establish noninferiority). An additional analysis will be performed based on the mITT population if there is enough difference between the mITT population and the evaluable population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
CCI	[redacted]

[redacted]

Endpoint	Statistical Analysis Methods
	CCI [redacted]

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	• Point estimates and exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the percentage of participants reporting each event (local reactions, systemic events, AEs, MAEs, and SAEs) for each vaccine group. • AEs and SAEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tiered approach will be used to summarize AEs. For both Tier 1 and Tier 2 events, the 95% CIs for the difference in the percentage of participants reporting the events between the RSV vaccine + Tdap group and the RSV vaccine + placebo group, and between the RSV vaccine + Tdap group and the placebo + Tdap group, will be calculated using the test statistic proposed by Miettinen and Nurminen. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. There are no preidentified Tier 1 events for this study. A MedDRA preferred term is defined as a Tier 2 event if there are 4 or more participants in at least 1 vaccine group reporting the event. Descriptive summary statistics (counts and percentages) will be provided for Tier 3 events for each vaccine group. The safety analyses are based on the safety population. Participants will be summarized according to the vaccine group corresponding to the investigational product they actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE severity will be addressed using the Pfizer safety rules.
Secondary	• N/A
CCI [redacted]	[redacted]

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. The analysis will be performed after all participants completed the study and when all of the data are available.

9.5.1. Data Monitoring Committee

This study will use an E-DMC.

Refer to the E-DMC charter for further details.

CCI [redacted]

[redacted]

[redacted].

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about her right to access and correct her personal data and to withdraw consent for the processing of her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan/contracts.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The

investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in site Source Data Agreement Plan.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Not applicable.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.2).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.2. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

A postmenopausal state is defined as no menses occurring for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range (as per the reference range used by the laboratory) may be used to confirm a postmenopausal state in women who are not using hormonal contraception or hormone replacement therapy (HRT).

- Females whose menopausal status is in doubt will be required to use one of the appropriate acceptable effective contraception methods described in Section 10.4.3.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

- Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

10.4.3. Contraception Methods

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Hormone-releasing intrauterine system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - oral;

   - intravaginal;

   - transdermal;

   - injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - oral;

   - injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

9. Progestogen only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

Collection of Pregnancy Information

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
$Al(OH)_3$	aluminum hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
dLIA	direct-binding Luminex immunoassay
DNA	deoxyribonucleic acid
DTaP	diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed
DTd	diphtheria toxoid
EC	ethics committee
ECG	electrocardiogram
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FHA	filamentous hemagglutinin
FIH	first-in-human
FI-RSV	formalin-inactivated respiratory syncytial virus vaccine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
H_0	null hypothesis
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure

Abbreviation	Term
ICD	informed consent document
ICH	International Council for Harmonisation
Ig	immunoglobulin
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	hormone-releasing intrauterine system
IWR	interactive Web-based response
Lf	limit(s) of flocculation
LFT	liver function test
LLOQ	lower limit of quantitation
LMIC	lower- and middle-income country
LRTI	lower respiratory tract illness
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
NaCl	sodium chloride
PCD	primary completion date
PRN	pertactin
PT	pertussis toxin
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
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
sWFI	sterile water for injection
TBili	total bilirubin
Td	tetanus and diphtheria toxoids adsorbed
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed
Tris	tromethamine, or tris(hydroxymethyl)aminomethane
TTd	tetanus toxoid
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

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