# A PHASE 3, RANDOMIZED, OPEN-LABEL TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE FORMULATED IN MULTIDOSE VIALS IN HEALTHY FEMALE ADULTS

| | |
|---|---|
| **Study Intervention Number:** | PF-07850720 |
| **Study Intervention Name:** | Respiratory Syncytial Virus (RSV) Vaccine |
| **US IND Number:** | 017931 |
| **EudraCT Number:** | Not applicable |
| **ClinicalTrials.gov ID:** | Not available |
| **Pediatric Investigational Plan Number:** | Not applicable |
| **Protocol Number:** | C4841001 |
| **Phase:** | 3 |
| **Sponsor Legal Address:** | Pfizer Inc.<br>66 Hudson Boulevard East<br>New York, NY 10001 |

**Brief Title:** Safety, Tolerability, and Immunogenicity Study of RSVpreF Multidose Vials in Healthy Female Adults

## Document History

| Document | Version Date |
|---|---|
| Amendment 1 | 26 Feb 2024 |
| Original protocol | 06 Dec 2023 |

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

## Protocol Amendment Summary of Changes Table

## Amendment 1 (26 February 2024)

## Overall Rationale for the Amendment:

To add a secondary immunogenicity objective in response to a regulatory request and address some nonsubstantial modifications to the protocol.

| Description of Change | Brief Rationale | Section # and Name |
|---|---|---|
| **Substantial Modification(s)** | | |
| Added a secondary immunogenicity objective. | In response to CBER request. | Section 1.1 Synopsis<br>Section 3 Objectives, Endpoints, and Estimands<br>Section 9.1.1.2.1 Immunogenicity<br>Section 9.3.3 Secondary Endpoint(s)/Estimand(s) Analysis |
| **Nonsubstantial Modification(s)** | | |
| Corrected the fever ranges. | Typographical error. | Section 8.3.5.4 Fever (Table 4) |
| Changed GMTs to GMCs and changed "titer" to "IgG level" in the exploratory endpoint. | For accuracy. | Section 9.3.4 Tertiary/Exploratory Endpoint(s) Analysis |
| Amended the Tier 2 event description. | For clarity. | Section 9.3.2.2 Safety |
| Removed the exploratory estimand description. | To align with the Pfizer protocol template. | Section 9.1.1.3. Exploratory Estimands |
| Updated the section to reflect the replacement of the emergency contact card with a study information card. | The process for contacting an MQI has changed from a medical escalation process via a Pfizer call center to direct clinical team contact using a Study Team Contact List.<br><br>The emergency contact card is being replaced by a study information card and will no longer be referenced. | Section 8.10.1 Visit 1 – Vaccination (Clinic, Day 1)<br>Section 10.1.12 Sponsor's Medically Qualified Individual<br>Section 10.7 Appendix 7: Abbreviations |

| Description of Change | Brief Rationale | Section # and Name |
|---|---|---|
| Updated the abbreviations list to remove ECC (emergency contact card) and add GMC (geometric mean concentration). | To reflect the changes in the document. | Section 10.7 Appendix 7: Abbreviations |

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# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

### Protocol Title:

A Phase 3, Randomized, Open-Label Trial to Evaluate the Safety, Tolerability, and Immunogenicity of Respiratory Syncytial Virus (RSV) Prefusion F Subunit Vaccine Formulated in Multidose Vials in Healthy Female Adults

### Brief Title:

Safety, Tolerability, and Immunogenicity Study of RSVpreF Multidose Vials in Healthy Female Adults

### Regulatory Agency Identification Number(s):

| | |
|---|---|
| **US IND Number:** | 017931 |
| **EudraCT Number:** | Not applicable |
| **ClinicalTrials.gov ID:** | Not available |
| **Pediatric Investigational Plan Number:** | Not applicable |
| **Protocol Number:** | C4841001 |
| **Phase:** | 3 |

### Rationale:

Pfizer has developed a vaccine to protect against respiratory syncytial virus (RSV) disease. The vaccine, respiratory syncytial virus stabilized prefusion F subunit vaccine (RSVpreF), contains 2 stabilized prefusion RSV F glycoproteins in equal amounts in a lyophilized dosage form for reconstitution. The efficacy and effectiveness of bivalent RSVpreF against RSV disease have been demonstrated in both older adult (Study C3671013) and maternal immunization (Study C3671008) clinical trials. Currently, RSVpreF is available preservative-free as a single-dose vial (SDV).

Vaccines are often offered in a multidose vial (MDV) presentation for use in low- and middle-income countries (LMICs) to meet the supply needs of national immunization program requirements. Pfizer has partnered with the Bill & Melinda Gates Foundation to increase access to immunization in LMICs by developing an MDV presentation of RSVpreF (3 doses per vial). In SDV presentations, each dose remains sealed and protected until it is ready for administration, decreasing chances for wastage and contamination. Because each dose needs its own container, single-dose presentations typically occupy a greater volume per dose with regard to supply chain storage and medical waste disposal. The advantage of MDVs is that they generally allow the vaccine to occupy less cold-chain capacity than single-dose presentations, therefore reducing cold-chain and storage costs. The MDV is reconstituted similarly to the SDV; however, the MDV diluent contains a preservative, 2-phenoxyethanol (2-PE), to prevent microbial growth from the first to the last dose administration per vial.

This study will compare the safety, tolerability, and immunogenicity of RSVpreF with 2-PE presented in MDVs to RSVpreF without 2-PE presented in SDVs.

**Objectives, Endpoints, and Estimands:**

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| **Immunogenicity** | | |
| To demonstrate that the immune responses elicited by MDV RSVpreF are noninferior to the immune responses in adults vaccinated with SDV RSVpreF. | • Respiratory syncytial virus subgroup A (RSV A) and respiratory syncytial virus subgroup B (RSV B) serum neutralizing titers (NTs). | In participants who received the study intervention and in compliance with the key protocol criteria (evaluable immunogenicity population):<br>• Geometric mean titer (GMT) ratio (GMR), estimated by the ratio of the GMTs for RSV A and RSV B NTs at 1 month after vaccination with RSVpreF in MDV participants to that of SDV participants. |
| **Safety** | | |
| To describe the safety profile of RSVpreF (MDV and SDV) as measured by the percentage of participants reporting local reactions, systemic events, adverse events (AEs), and serious adverse events (SAEs) following study intervention administration. | • Local reactions (pain at the injection site, redness, and swelling).<br>• Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain).<br>• AEs.<br>• SAEs. | In participants receiving the study intervention:<br>• The proportion of participants reporting local reactions within 7 days following study intervention administration.<br>• The proportion of participants reporting systemic events within 7 days following study intervention administration.<br>• The proportion of participants reporting AEs through 1 month following study intervention administration.<br>• The proportion of participants reporting SAEs throughout the study. |
| **Secondary:** | **Secondary:** | **Secondary:** |
| To describe the immune response elicited by MDV RSVpreF compared to the immune response elicited by SDV RSVpreF. | • RSV A and RSV B serum NTs. | In participants who received the study intervention and in compliance with the key protocol criteria (evaluable immunogenicity population):<br>• Seroresponse rates, by vaccine group, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the prevaccination titer; or ≥4 times the lower limit of quantitation (LLOQ) if the prevaccination titer is below the LLOQ. |

**Overall Design:**

This is a Phase 3, randomized (1:1), open-label study to evaluate the safety, tolerability, and immunogenicity of RSVpreF with 2-PE formulated in MDVs compared to RSVpreF without 2-PE formulated in SDVs. Approximately 452 healthy nonpregnant, nonbreastfeeding female participants will be enrolled in the study within the United States (US). The total duration for each participant will be approximately 6 weeks.

**Number of Participants:**

Approximately 452 female participants will be enrolled in the study.

**Note:** "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention.

**Study Population:**

Key inclusion and exclusion criteria are listed below:

**Inclusion Criteria**

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

- Healthy nonpregnant, nonbreastfeeding females 18 through 49 years of age at Visit 1 (Day 1).

  **Note:** Healthy female 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. Specific criteria for participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in the protocol.

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

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

**Exclusion Criteria**

Participants with any of the following characteristics/conditions will be excluded:

- Any medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality, that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

- 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.

- History or active autoimmune disease, 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).

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

- Receipt of chronic systemic treatment with immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment through conclusion of the study.

  **Note:** 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 study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

- Receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration or planned receipt throughout the study.

- Current alcohol abuse or illicit drug use.

  **Note:** Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some states.

- Individuals who are pregnant or breastfeeding.

- Participation in other studies involving an investigational product within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

## Study Arms and Duration:

| Study Intervention(s) | | |
|---|---|---|
| **Intervention Name** | **RSVpreF With 2-PE (MDV) PF-07850720** | **RSVpreF Without 2-PE (SDV) PF-06928316** |
| **Use** | Experimental | Experimental |
| **Investigational Medicinal Product (IMP) or Noninvestigational Medicinal Product (NIMP)/Auxiliary Medicinal Product (AxMP)** | IMP | IMP |
| **Dose Formulation** | RSV vaccine 360 µg lyophilized powder for solution for injection/vial | RSV vaccine 120 µg lyophilized powder for solution for injection/vial |
| **Unit Dose Strength(s)** | 120 µg | |
| **Route of Administration** | Intramuscular injection (deltoid muscle of the nondominant arm [preferred]) | |
| **Study Arm(s)** | | |
| **Arm Title** | **RSVpreF With 2-PE** | **RSVpreF Without 2-PE** |
| **Arm Description** | Three doses of RSVpreF will be contained within each MDV. For the purposes of this study, only a single 0.5-mL dose (120 µg) will be administered from each of the MDVs; the rest will be discarded. Participants will receive RSVpreF (120 µg) reconstituted with a sterile water diluent containing 2-PE, presented in a vial. The RSVpreF dose will be administered once at the vaccination visit (Day 1). | Participants will receive RSVpreF (120 µg) reconstituted with a PFS of sterile water diluent. The RSVpreF dose will be administered once at the vaccination visit (Day 1). |

## Study Duration:

Participants will participate in the study for approximately 6 weeks.

## 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 for the primary endpoints can be found in the protocol. The study sample size is based upon the evaluation of noninferiority (NI) of RSVpreF in the MDV group to RSVpreF in the SDV group on the primary endpoint. Noninferiority will be evaluated using a 1.5-fold margin as the criterion. The NI of RSVpreF in the MDV group with respect to the SDV group will be evaluated at 1 month after vaccination for RSV A and RSV B NTs. Calculation details are presented in the protocol.

The primary objective of NI will be met only if the statistical criteria for both RSV A and RSV B are met. Therefore, no multiplicity adjustment is needed.

No interim analysis is planned for this study.

**Ethical Considerations:**

The available safety, immunogenicity, and effectiveness data from ongoing clinical trials for RSVpreF support a favorable benefit/risk profile and support the clinical development of the MDV presentation. The available safety data from various vaccines that currently are used with 2-PE as a preservative also support a favorable benefit/risk profile. Considering the measures to minimize risk to study participants, the potential risks identified in association with the study intervention are justified by the anticipated benefits that may be afforded to participants in this study.

RSVpreF contains F glycoproteins stabilized in the prefusion conformation, elicits strong neutralizing antibodies, and has demonstrated efficacy against RSV-associated lower respiratory tract illness (LRTI-RSV) in older adults and severe LRTI-RSV in infants born to vaccinated maternal participants. The preservative in the MDV, 2-PE, is used to control potential microbial contamination following RSVpreF reconstitution, thereby extending the storage time of the vaccine. Anticipated AEs after vaccination with RSVpreF with 2-PE are expected to be similar to those observed following vaccination with SDV RSVpreF (mild to moderate reactogenicity), which are manageable using routine symptom-driven standard of care.

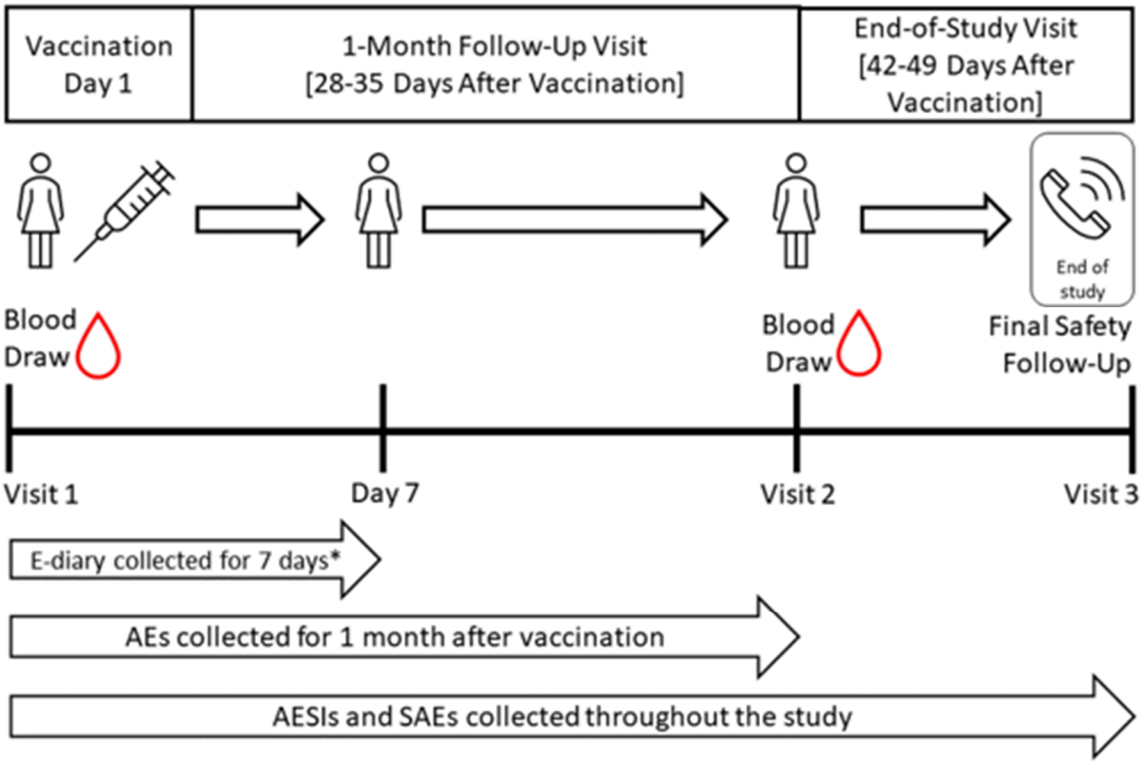
Based on the experience with RSVpreF, the potential risks are:

- Local reactions, such as injection site redness, injection site swelling, and injection site pain; systemic events, such as fatigue, headache, muscle pain, and joint pain; and fever.
- Guillain-Barré syndrome. In Study C3671013, conducted in adults 60 years of age and older, there were 2 cases of Guillain-Barré syndrome or its variants identified with a plausible temporal relationship with vaccination among >18,000 individuals who received RSVpreF. Both cases had confounding factors or alternative etiology.
- Other events of special interest include atrial fibrillation and polyneuropathy.

The study procedure-related risks include:

- Venipuncture will be performed during the study.

## 1.2. Schema




**E-diary will capture local reaction and systemic event data during the 7-day follow-up period or longer for ongoing local reactions and systemic events after study vaccination (ie, from Day 1, the day of vaccination, until event resolution). After e-diary collection, the site will follow up with the participant for any ongoing events.*

### 1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section 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.

**Table 1. Study Schedule of Assessment**

| **Visit Number** Abbreviations used in this table may be found in Appendix 7. | **1** | **2** | **3** | **Notes** |
|---|---|---|---|---|
| **Visit Description** | **Vaccination** | **1-Month Follow-Up Visit** | **End-of-Study Visit** | |
| **Visit Window (Days)** | **Day 1** | **28 to 35 Days After Vaccination** | **42 to 49 Days After Vaccination** | Day relative to start of study intervention administration (Day 1). |
| **Type of Visit** | **Clinic** | **Clinic** | **Telephone** | |
| Obtain informed consent | X | | | • Informed consent should be obtained prior to undergoing any study-specific procedures.<br>• See Section 10.1.3 for additional information. |
| Assign single participant identifier | X | | | |
| Obtain demography and significant medical history data | X | | | |
| Record height, weight, and vital signs (blood pressure, pulse rate) | X | | | |
| Perform clinical assessment (and physical examination if deemed necessary) | X | | | • See Section 8.3.1 for additional information.<br>• Physical examinations to be completed before administration of study intervention. |
| Perform urine pregnancy test on WOCBP | X | | | See Section 8.3.4 for additional information. |
| Confirm use of contraceptives (if appropriate) | X | | | See Section 5.3.1 for additional information. |

## Table 1. Study Schedule of Assessment

| **Visit Number**<br>Abbreviations used in this table may be found in Appendix 7. | **1** | **2** | **3** | **Notes** |
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| **Visit Description** | **Vaccination** | **1-Month Follow-Up Visit** | **End-of-Study Visit** | |
| **Visit Window (Days)** | **Day 1** | **28 to 35 Days After Vaccination** | **42 to 49 Days After Vaccination** | Day relative to start of study intervention administration (Day 1). |
| **Type of Visit** | **Clinic** | **Clinic** | **Telephone** | |
| Collect nonstudy vaccine information | X | X | X | See Section 6.9 for additional information. |
| Collect prohibited medications and treatments | X | X | X | See Section 6.9 for additional information. |
| Confirm inclusion and exclusion criteria | X | | | |
| Obtain prevaccination temperature | X | | | |
| Review temporary delay criteria | X | | | |
| Assign randomization and container number | X | | | |
| Obtain blood sample for antibody assessment (~20 mL) | X | X | | |
| Assist the participant in downloading the e-diary application onto her own device or issue a provisioned device for e-diary use | X | | | See Section 8.3.5 for more information. |
| Study intervention administration | X | | | See Section 6.1 for additional information. |
| Postvaccination observation (at least 30 minutes) and assessment of immediate adverse reactions | X | | | |
| Dispense measuring device and digital thermometer | X | | | |

## Table 1. Study Schedule of Assessment

| **Visit Number**<br>Abbreviations used in this table may be found in Appendix 7. | **1** | **2** | **3** | **Notes** |
|---|---|---|---|---|
| **Visit Description** | **Vaccination** | **1-Month Follow-Up Visit** | **End-of-Study Visit** | |
| **Visit Window (Days)** | **Day 1** | **28 to 35 Days After Vaccination** | **42 to 49 Days After Vaccination** | Day relative to start of study intervention administration (Day 1). |
| **Type of Visit** | **Clinic** | **Clinic** | **Telephone** | |
| Provide e-diary training on daily reactogenicity questionnaire | X | | | |
| Site review of e-diary data with participant follow-up until ongoing event resolution, if applicable | X----------X | | | • Local reactions and systemic events will be captured within the e-diary until the resolution date.<br>• Site staff to evaluate participant compliance and as part of the ongoing safety review following vaccination.<br>• After e-diary collection, the site will follow up with the participant for any ongoing events. |
| Record AEs, as appropriate | X | X | | See Section 8.4 for additional information. |
| Record AESIs, as appropriate | X | X | X | See Section 8.4 for additional information. |
| Record SAEs, as appropriate | X | X | X | See Section 8.4 for additional information. |
| Collect e-diary device/assist participant with deletion of e-diary application from personal device, as appropriate | | X | | Ensure all e-diary data have been transferred prior to e-diary deactivation or removal of the app. |

## 2. INTRODUCTION

Pfizer developed a vaccine to protect against RSV disease. The vaccine, RSVpreF, contains 2 stabilized prefusion RSV F glycoproteins in equal amounts in a lyophilized dosage form for reconstitution. The efficacy and effectiveness of RSVpreF against RSV disease have been demonstrated in older adult[1] (Study C3671013) and maternal immunization[2,3] (Studies C3671003, C3671008) clinical trials. Currently, RSVpreF is available preservative free as an SDV presentation.

Vaccines are often offered in an MDV presentation for use in LMICs to meet the supply needs of national immunization program requirements. Pfizer has partnered with the Bill & Melinda Gates Foundation to increase access to immunization in LMICs by developing an MDV presentation of RSVpreF (3 doses per vial). In SDV presentations, each dose remains sealed and protected until it is ready for administration, decreasing chances for wastage and contamination. Because each dose needs its own container, single-dose presentations typically occupy a greater volume per dose with regard to supply chain storage and medical waste disposal.[4,5] This issue is a significant problem when storage and transport space are limited. The advantage of multidose vials is that they generally allow the vaccine to occupy less cold-chain capacity than single-dose presentations, therefore reducing cold-chain and storage costs.[6] Unlike SDVs that are discarded immediately after single use, MDVs are used more than once after the vial is opened. As the vaccine vial is repeatedly used, a preservative not present in single-dose syringes is required. 2-Phenoxyethanol is the preservative that will be added to the RSVpreF vaccine in MDVs in order to prevent microbial growth. This preservative is a phenolic derivative used as a preservative in a number of commercially available vaccines.[7]

### 2.1. Study Rationale

Studies have shown nonpregnant and pregnant individuals vaccinated with RSVpreF to have an elevated immune response to RSVpreF.[2,8] To streamline and expedite the availability of the MDV presentation in LMICs, this study will be conducted with nonpregnant individuals. Study C4841001 will compare the safety, tolerability, and immunogenicity of RSVpreF with 2-PE presented in MDVs to RSVpreF without 2-PE presented in SDVs.

### 2.2. Background

The vaccine investigated in this study is a bivalent RSV prefusion F subunit vaccine (RSVpreF) developed by Pfizer. The RSV F glycoprotein facilitates fusion of the virion and host cell membrane through a transition from an unstable but highly immunogenic prefusion conformation to the more stable postfusion state.[9] Preclinical studies show that prefusion F elicits much higher NTs than postfusion F and that the most potent neutralizing antibodies from postinfection human sera target the prefusion form.[10] RSVpreF is composed of engineered, stabilized, trimeric, prefusion F glycoproteins matching the 2 subgroups (RSV A and B) to help ensure the broadest coverage against RSV illness.

RSVpreF development started with 2 indications using the same antigens, dose, and formulation:

- **Older Adult:** Prevention of LRTI-RSV in adults 60 years of age and older via active immunization.

- **Maternal:** Prevention of LRTI-RSV and severe LRTI-RSV in infants by active immunization of pregnant individuals.

As of November 2023, RSVpreF in the single-dose form has been studied in 7 completed trials in healthy adults and pregnant individuals, and 2 ongoing Phase 3 clinical trials in older adults. RSVpreF was shown to be well tolerated, with an acceptable safety profile, and highly efficacious in older adults and infants of individuals vaccinated during pregnancy. This will be the first study of the MDV.

The efficacy and effectiveness of RSVpreF against RSV disease has been demonstrated in older adult[1] (Study C3671013) and maternal immunization[2,3] (Studies C3671003, C3671008) clinical trials. RSVpreF (Abrysvo™) was approved for marketing in the US for the older adult population on 31 May 2023[11] and for pregnant individuals on 21 August 2023.[12] On 23 August 2023, RSVpreF (Abrysvo) was granted marketing authorization within the EU for the older adult population and for pregnant individuals.[13]

### 2.2.1. Clinical Overview

**Adult Program Studies**

The older adult program includes 2 Phase 1/2 studies, 3 Phase 3 studies, and a Phase 2a human challenge study.

- In the completed Phase 1/2 Study C3671001, 1233 healthy adults 18 through 49 and 50 through 85 years of age received the 3 dose levels of RSVpreF (60 µg, 120 µg, and 240 µg), with or without $Al(OH)_3$, or placebo, administered with or without concomitant influenza vaccine. The results have shown that the vaccine was well tolerated and immunogenic in both age groups. RSVpreF elicited robust neutralizing responses against RSV A and RSV B 1 month after vaccination for both age groups across all vaccine dose levels and formulations; these responses remained high through the 12 months after vaccination. RSVpreF was safe and well tolerated when administered alone or with SIIV, with no major differences observed across all dose levels and formulations. Most reported local reactions or systemic events were mild or moderate in severity. The proportions of participants reporting AEs were generally similar across RSVpreF groups, and no SAEs were considered related to the investigational vaccine.[14]

- In the completed Phase 1/2 Study C3671002, 250 older adults 65 through 85 years of age received the 3 dose levels of RSVpreF (60 µg, 120 µg, and 240 µg) with $Al(OH)_3$ or $CpG/Al(OH)_3$, given as a single dose or on a schedule of 2 doses administered 2 months apart. All RSVpreF doses and formulations elicited high RSV A– and RSV B–neutralizing antibody GMTs 1 month after vaccination (GMFRs ranging from 4.8 to 11.6 and 4.5 to 14.1, respectively). CpG-containing formulations did not further increase neutralizing antibody GMTs compared to RSVpreF with or without $Al(OH)_3$. GMTs in all groups declined but remained higher than baseline (before vaccination) and placebo (SIIV only) 12 months after vaccination (GMFRs ranging from 2.1 to 3.5 and 2.2 to 4.3, respectively). No increase in GMTs was observed 1 month after Vaccination 2 (GMFR of 0.9). All doses and formulations were safe and well tolerated.[15]

- Study C3671014 is a completed Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind, lot-consistency study in a population of up to 1000 healthy adults 18 through 49 years of age. The study examined the immune response and the safety and tolerability profiles across 3 manufactured lots of RSVpreF when administered as a single 120-µg dose to healthy adults. The primary analyses showed that the ratios of neutralizing antibody GMTs for the 3 manufactured RSVpreF lots 1 month after vaccination were equivalent, and that the 120-µg dose of RSVpreF was well tolerated and has an acceptable safety profile.

- A Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, immunogenicity, and efficacy of an RSV vaccine (RSVpreF) in a virus challenge model in healthy adults (NCT04785612) was conducted by hVIVO in 70 participants 18 to 50 years of age. Participants received a single dose of either RSVpreF 120 µg or placebo, and 4 weeks later underwent intranasal challenge with RSV-A Memphis 37b virus. The immunogenicity and efficacy of RSVpreF vaccination on virus replication, clinical symptoms, and incidence of symptomatic RSV infection following the intranasal challenge were evaluated. The primary analysis of the human challenge study showed that a 120-µg dose of RSVpreF was well tolerated and has an acceptable safety profile. The completed study demonstrated 100% efficacy of RSVpreF against RT-PCR–confirmed symptomatic infection.[16]

- Study C3671013 is an ongoing Phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety, immunogenicity, and efficacy of Pfizer's RSVpreF in prevention of LRTI-RSV in adults 60 years of age and older. Both healthy adults and adults with stable chronic cardiopulmonary conditions are included. Approximately 10% of participants with stable chronic cardiopulmonary conditions such as COPD, asthma, or CHF have been enrolled. The study enrolled over 37,000 participants, randomized to receive RSVpreF or placebo in a 1:1 ratio. This is an event-driven study with a target of 59 first episodes of evaluable LRTI-RSV cases. Interim analysis results in August 2022 showed protection against LRTI-RSV defined by 2 or more symptoms, with VE of 66.7%. VE of 85.7% was observed in participants with a more severe disease primary endpoint of LRTI-RSV, defined by analysis of 3 or more RSV-associated symptoms. The vaccine was well tolerated, with no safety concerns.[1]

On 31 May 2023, the FDA approved RSVpreF (Abrysvo) for individuals 60 years of age and older in the US.[11] On 23 August 2023, RSVpreF (Abrysvo) was also granted marketing authorization within the EU for active immunization of adults 60 years of age and older for the prevention of LRTD caused by RSV.[13]

- Study C3671006 is a completed Phase 3, multicenter, parallel-group, placebo-controlled, randomized, double-blind study. One thousand four hundred three healthy adults ≥65 years of age were randomized in a 1:1 ratio to either a coadministration group or a sequential-administration group. The intention of this study was to demonstrate that the immune responses generated when a 120-µg dose of RSVpreF was coadministered with SIIV were noninferior to the immune responses generated when these products were administered 4 weeks apart. The safety and tolerability of RSVpreF were also examined. Results demonstrated NI of the RSVpreF and SIIV immune responses when RSVpreF was coadministered with SIIV. The results of this study support the acceptability of coadministration of RSVpreF and SIIV in an older adult population.

- Study C3671016 is an ongoing Phase 1/2/3 study of RSVpreF in participants 2 to <18 years of age at high risk of RSV disease that was initiated in June 2023. The study will consist of 2 phases: Phase 1 and Phase 2/3. Phase 1 is an open-label, age-descending, dose-finding study to assess the safety, tolerability, and immunogenicity of RSVpreF in children. Phase 1 will evaluate 2 doses—120 µg and 60 µg—in children 5 to <18 years and 2 to <5 years of age who are either healthy or have high risk chronic medical conditions. Participants have been enrolled in Phase 1 and will be followed for 6 months after vaccination. Safety and immunogenicity will be assessed prior to selecting a dose and commencing Phase 2/3. Phase 2/3 is a placebo-controlled, randomized, double-blind study to evaluate the safety, tolerability, and immunogenicity of RSVpreF based on dose selection activities from the Phase 1 study.

- Study C3671023 is an ongoing Phase 3 study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults at high risk of severe RSV disease in 2 distinct patient populations. Study C3671023 – Substudy A is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in adults 18 to <60 years of age considered to be at high risk of RSV disease due to certain chronic medical conditions, and Study C3671023 – Substudy B is a Phase 3, single-arm, open-label, multicenter study that will assess the safety, tolerability, and immunogenicity of Pfizer's RSVpreF in immunocompromised adults. The 120-µg dose will be evaluated in both substudies.

**Maternal Participant Program Studies**

RSVpreF is also being studied in the maternal program, which includes 2 Phase 2b studies and a Phase 3 study in nonpregnant and pregnant participants.

- Study C3671003 is a completed Phase 2b multicenter, randomized, placebo-controlled study. Up to 650 healthy pregnant individuals 18 through 49 years of age received RSVpreF (120 µg or 240 µg), formulated with or without $Al(OH)_3$, or placebo. The completed final analysis provided evidence of the good tolerability and safety of RSVpreF in maternal vaccine recipients and the safety of maternal vaccination with RSVpreF for infants led to a dose selection of RSVpreF 120 µg without $Al(OH)_3$.

- Study C3671004 is a completed Phase 2b study of 713 healthy nonpregnant individuals 18 through 49 years of age. A total of 709 participants received RSVpreF 120 µg or RSVpreF 240 µg with $Al(OH)_3$ or placebo, administered with or without concomitant Tdap. The study demonstrated a good safety and tolerability profile, high immune responses, and NI of the responses to RSV A, RSV B, tetanus, and diphtheria when coadministered with Tdap, with RSV A and RSV B 50% NT GMRs of 0.97 and 0.96, respectively, at 1 month after vaccination.[8]

- Study C3671008 is a completed Phase 3, multicenter, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of maternal immunization with RSVpreF against MA-LRTI in infants. Healthy participants ≤49 years of age at 24 through 36 weeks' gestation received either RSVpreF 120 µg or placebo. The study enrolled approximately 7400 pregnant individuals.[3,17] Interim analysis results in October 2022 demonstrated VE of 81.8% against severe MA-LRTI due to RSV in infants from birth through the first 90 days of life, with high efficacy of 69.4% demonstrated through the first 6 months of life. RSVpreF was well tolerated with no safety concerns for both vaccinated individuals and their newborns.[3] On 21 August 2023, the FDA approved RSVpreF (Abrysvo) for active immunization of pregnant individuals at 32 through 36 weeks' gestation for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age in the US.[12] On 23 August 2023, RSVpreF (Abrysvo) was granted marketing authorization within the EU for passive protection against LRTD caused by RSV in infants from birth through 6 months of age following maternal immunization during pregnancy.[13]

## 2.3. Benefit/Risk Assessment

The available safety, immunogenicity, and effectiveness data from ongoing clinical trials for RSVpreF support a favorable benefit/risk profile.

When using multidose containers, preservatives are necessary to prevent contamination of future doses extracted from the same vial after the first dose. The risk of infection due to administration of a contaminated dose far outweighs the risk of any AE from the preservative used. In this case, 2-PE, the preservative used to control microbial contamination in the MDV, is a widely used preservative in cosmetics and vaccines, and one that already meets strict EP and WHO criteria for antimicrobial suppression and open-vial policy.[18] Many licensed vaccines **containing** 2-PE (eg, poliovirus vaccine inactivated [Ipol]); pneumococcal vaccines [Prevnar 13®]; diphtheria, tetanus, and pertussis–containing vaccines [DTwP and DT acellular]; hexavalent vaccines) have been shown to be immunogenic and safe.[19,20] Many other vaccines in development are using 2-PE due to its safety profile.[21]

MDV RSVpreF will support the clinical development of the vaccine and improve RSVpreF availability and accessibility in resource-limited countries. Anticipated AEs after vaccination are expected to be similar to those observed following vaccination with SDV RSVpreF (mild to moderate reactogenicity), which are manageable using routine symptom-driven standard of care. The expected safety profile of this vaccine therefore supports initiation of this clinical study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of RSVpreF may be found in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

### 2.3.1. Risk Assessment

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s)<br>RSVpreF (SDV) & RSVpreF with 2-PE (MDV)** | | |
| Pfizer has identified the most common risks for RSVpreF as local reactions, such as injection site redness, injection site swelling, and injection site pain, and systemic events, such as fatigue, headache, diarrhea, joint pain, nausea, vomiting, muscle pain, and fever.<br><br>Guillain-Barré syndrome has been identified as a potential risk for RSVpreF.<br><br>Other events of interest include atrial fibrillation and polyneuropathy.<br><br>The identified adverse reactions in local product labels may vary depending on the requirements of the respective regulatory authorities (eg, EU-SmPC and USPI). | These are common adverse reactions seen with other vaccines as well as RSVpreF.[22]<br><br>Data available from completed and ongoing studies showed a low incidence of severe or serious events, and no clinically concerning safety observations.[23,24] The vaccine appears to be safe and well tolerated across the safety population and within demographic subgroups based on age, sex, and race/ethnicity.<br><br>In Study C3671013, conducted in adults 60 years of age and older, there were 2 cases of Guillain-Barré syndrome or its variants with a plausible temporal relationship, with vaccination among >18,000 individuals who received RSVpreF. Both cases had confounding factors or alternative etiology.<br><br>In Study C3671013, conducted in adults 60 years of age and older, there was a nonsignificant numerical imbalance in the number of cases of atrial fibrillation reported for individuals who received RSVpreF compared to individuals who received the placebo. Most of the participants who had atrial fibrillation and received RSVpreF had a preexisting medical history of atrial fibrillation.<br><br>In Study C3671008, conducted in pregnant individuals, there were no statistically meaningful imbalances between RSVpreF and placebo recipients in the overall rates of preterm birth (5.7% [95% CI: 4.9, 6.5] versus 4.7% [95% CI: 4.1, 5.5], respectively). However, a numerical imbalance was observed in upper-middle-income countries between RSVpreF and placebo recipients. Outcomes in the premature infants were similar between the 2 groups. | • The study employs the use of a reactogenicity e-diary, which allows the investigator to monitor local reactions and systemic events in real time through an electronic portal. Severe reactions will require an unscheduled telephone call to determine if an unscheduled visit is required to be conducted per protocol.<br><br>• All study participants will be observed for at least 30 minutes after vaccination.<br><br>• AEs and SAEs will be collected at specified time points throughout the study.<br><br>• Specific references to risks and events of interest are made within the ICD, with reporting instructions if a case is suspected. |

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s)<br>RSVpreF (SDV) & RSVpreF with 2-PE (MDV)** | | |
| | In Study C3671008, conducted in pregnant individuals, there was a nonsignificant numerical imbalance in hypertensive disorders of pregnancy reported for participants who received RSVpreF compared to participants who received the placebo.<br><br>The majority of preterm and hypertensive disorders occurred more than 30 days following vaccination. | |
| **Study Procedures** | | |
| Venipuncture will be performed during the study. | There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site. | Only appropriately qualified personnel will obtain the blood draw. |

### 2.3.2. Benefit Assessment

Benefits to individual participants enrolled may be:

- Receipt of a potentially efficacious RSV vaccine.
- Contributing to the process of developing new therapies in an area of unmet need.

### 2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with RSVpreF are justified by the anticipated benefits that may be afforded to participants.

## 3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Primary:** | **Primary:** | **Primary:** |
| **Immunogenicity** | | |
| To demonstrate that the immune responses elicited by MDV RSVpreF are noninferior to the immune responses in adults vaccinated with SDV RSVpreF. | • RSV A and RSV B serum NTs. | In participants who received the study intervention and in compliance with the key protocol criteria (evaluable immunogenicity population):<br>• GMT ratio (GMR), estimated by the ratio of the GMTs for RSV A and RSV B serum NTs at 1 month after vaccination with RSVpreF in MDV participants to that of SDV participants. |
| **Safety** | | |
| To describe the safety profile of RSVpreF (MDV and SDV) as measured by the percentage of participants reporting local reactions, systemic events, AEs, and SAEs following study intervention administration. | • Local reactions (pain at the injection site, redness, and swelling).<br>• Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain).<br>• AEs.<br>• SAEs. | In participants receiving the study intervention:<br>• The proportion of participants reporting local reactions within 7 days following study intervention administration.<br>• The proportion of participants reporting systemic events within 7 days following study intervention administration.<br>• The proportion of participants reporting AEs through 1 month following study intervention administration.<br>• The proportion of participants reporting SAEs throughout the study. |

| Objectives | Endpoints | Estimands |
|---|---|---|
| **Secondary:** | **Secondary:** | **Secondary:** |
| To describe the immune response elicited by MDV RSVpreF compared to the immune response elicited by SDV RSVpreF. | • RSV A and RSV B serum NTs. | In participants who received the study intervention and in compliance with the key protocol criteria (evaluable immunogenicity population):<br>• Seroresponse rates, by vaccine group, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the prevaccination titer; or ≥4 times the LLOQ if the prevaccination titer is below the LLOQ. |
| **Exploratory:** | **Exploratory:** | **Exploratory:** |
| To further describe the immune responses induced by MDV RSVpreF following vaccination. | • RSV A and RSV B prefusion F–binding IgG. | Not applicable. |

# 4. STUDY DESIGN

## 4.1. Overall Design

This is a Phase 3, randomized, open-label study to evaluate the safety, tolerability, and immunogenicity of RSVpreF with 2-PE formulated in MDVs compared to RSVpreF without 2-PE formulated in SDVs. Approximately 452 healthy nonpregnant, nonbreastfeeding female participants 18 through 49 years of age will be enrolled and randomized in a 1:1 ratio in the study within the US. The total duration for each participant will be approximately 6 weeks.

**Note:** "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention.

## 4.2. Scientific Rationale for Study Design

Vaccines are often presented in an MDV for use in developing countries. The advantage of MDVs is that they allow the vaccine to occupy less cold-chain capacity than SDS or SDV presentations. Pfizer has partnered with the Bill & Melinda Gates Foundation to increase access to immunization in LMICs by developing an MDV presentation of RSVpreF. As the vaccine vial is repeatedly used, a preservative (2-PE) that is not present in SDVs will be added to prevent microbial growth.

This study will compare the safety, tolerability, and immunogenicity of RSVpreF with 2-PE in MDVs to RSVpreF without 2-PE in SDVs.

### 4.2.1. Diversity of Study Population

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. The diversity strategy for this study will include the following:

- Selecting sites that have access to diverse participants within their locales.
- Educating sites about the importance of increasing diversity in clinical trials and Pfizer's commitments to diversity and inclusion.
- Using real-world data to target outreach and potential referring physicians.
- Continual monitoring of diverse enrollment to identify additional opportunities to include diverse populations.

### 4.2.2. Choice of Contraception/Barrier Requirements

RSVpreF is approved for use in the US and Europe, as detailed in Section 4.3, without any contraceptive precautions. There is no suspicion of human teratogenicity based on the intended pharmacology. See Appendix 3 for contraceptive requirements.

## 4.3. Justification for Dose

The 120-µg dose, without any adjuvants, has been shown to have low reactogenicity and an acceptable safety profile, and will be the dose given in this study. RSVpreF has been licensed for use in the US in older adults on 31 May 2023[11] and for pregnant individuals on 21 August 2023.[12] On 23 August 2023, RSVpreF (Abrysvo) was granted marketing authorization within the EU for the older adult population and for pregnant individuals.[13] MDVs reduce the cold-chain capacity and the delivery and storage costs associated with SDV vaccines in LMICs. The preservative 2-PE will be used to prevent microbial growth in MDVs following reconstitution.

## 4.4. End of Study Definition

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

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit.

# 5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. 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 this study only if all of the following criteria apply:

**Age and Sex:**

1. Healthy nonpregnant, nonbreastfeeding females 18 through 49 years of age at Visit 1 (Day 1).

   **Note:** Healthy female 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. Specific criteria for participants with known stable infection with HIV, HCV, or HBV can be found in Section 10.6.

   - Refer to Appendix 3 for reproductive criteria for female participants.

**Disease Characteristics:**

Not applicable.

**Other Inclusion Criteria:**

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

3. Available for the duration of the study and can be contacted by telephone during study participation.

4. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3), which includes compliance with the requirements and restrictions listed in the 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. Any medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality, that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. 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.

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

4. History or active autoimmune disease, 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).

5. Bleeding diathesis or any condition that would, in the opinion of the investigator, contraindicate intramuscular injection.

**Prior/Concomitant Therapy:**

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

7. Receipt of chronic systemic treatment with immunosuppressant medications (including cytotoxic agents or systemic corticosteroids), or radiotherapy, within 60 days before enrollment through conclusion of the study.

   **Note:** 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 study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

8. Receipt of blood/plasma products or immunoglobulin within 60 days before study intervention administration or planned receipt throughout the study.

9. Current alcohol abuse or illicit drug use.

**Note:** Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some states.

10. Individuals who are pregnant or breastfeeding.

**Prior/Concurrent Clinical Study Experience:**

11. Participation in other studies involving an investigational product within 28 days prior to study entry and/or during study participation. Participation in purely observational studies is acceptable.

**Diagnostic Assessments:**

Not applicable.

**Other Exclusion Criteria:**

12. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

### 5.3. Lifestyle Considerations

#### 5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Section 10.3.3) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable 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, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

All pregnancies discovered in participants during the study participation, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded in accordance with the EDP (Section 8.4.5.1) and EDB (Section 8.4.5.2) reporting processes.

### 5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any AEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number once eligibility criteria are met. Participants who are rescreened are required to sign a new ICD.

### 5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

The following conditions may allow a participant to be randomized once the conditions have resolved and the participant is otherwise eligible:

1. Current febrile illness (body temperature >38.0°C [>100.4°F]) or other acute illness within 48 hours before study intervention 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, study intervention administration.

3. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention 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 study intervention administration.

**The prevaccination blood draw and vaccination should take place on the same day.**

## 6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational products and medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to RSVpreF with the preservative 2-PE presented in MDVs and RSVpreF without 2-PE in SDVs.

## 6.1. Study Intervention(s) Administered

| Study Intervention(s) | | |
|---|---|---|
| **Intervention Name** | **RSVpreF with 2-PE (MDV) PF-07850720** | **RSVpreF without 2-PE (SDV) PF-06928316** |
| **Type** | Vaccine | Vaccine |
| **Use** | Experimental | Experimental |
| **IMP or NIMP/AxMP** | IMP | IMP |
| **Dose Formulation** | RSV vaccine 360 µg lyophilized powder for solution for injection/vial | RSV vaccine 120 µg lyophilized powder for solution for injection/vial |
| **Unit Dose Strength(s)** | 120 µg | |
| **Dosage Level(s)** | RSVpreF 120 µg | |
| **Route of Administration** | Intramuscular injection (deltoid muscle of the nondominant arm [preferred]) | Intramuscular injection (deltoid muscle of the nondominant arm [preferred]) |
| **Sourcing** | Provided centrally by Pfizer | Provided centrally by Pfizer |
| **Packaging and Labeling** | Study intervention will be provided in a glass vial as an open-label supply.<br>The RSV drug product MDV will contain 3 doses of 120 µg per dose of the RSVpreF antigens. RSVpreF is supplied as a lyophilized white cake, packaged in a glass vial with a 13-mm lyophilization stopper, aluminum overseal, and flip-off cap. It is reconstituted with a sterile water diluent consisting of 2-PE (preservative) in a glass vial. The lyophilized drug product contains excipients that, after reconstitution, will yield a solution as detailed in the IB.<br><br>The fill volume of the drug product vial and diluent vials are designed to ensure that each vial can supply 3 doses of vaccine and 120 µg for each dose. Each kit will be labeled as required per country requirement.<br><br>The vaccine will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements. | Study intervention will be provided in a glass vial as an open-label supply.<br>The RSV drug product SDV will contain a single dose of 120 µg of the RSVpreF antigens. RSVpreF is supplied as a lyophilized white cake, packaged in a clear glass 2-mL vial with a rubber stopper, aluminum overseal, and flip-off cap. It is reconstituted with a PFS of sterile water diluent for injection and a vial adaptor (supplied). Each kit will be labeled as required per country requirement.<br><br>The vaccine will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements. |
| **SRSD** | IB | IB/SmPC |

| Study Intervention(s) | | |
|---|---|---|
| Study Arm(s) | | |
| **Arm Title** | **RSVpreF With 2-PE** | **RSVpreF Without 2-PE** |
| **Arm Description** | Three doses of RSVpreF will be contained within each MDV. For the purposes of this study, only a single 0.5-mL dose (120 µg) will be administered from each of the MDVs; the rest will be discarded. Participants will receive RSVpreF (120 µg) reconstituted with a sterile water diluent containing 2-PE, presented in a vial, in accordance with the IPM.<br><br>The RSVpreF dose will be administered once at the vaccination visit (Day 1). | Participants will receive RSVpreF (120 µg) reconstituted with a PFS of sterile water diluent in accordance with the IPM.<br><br>The RSVpreF dose will be administered once at the vaccination visit (Day 1). |

### 6.1.1. Administration

Participants will receive 1 dose of study intervention at the vaccination visit (Day 1) in accordance with the study's SoA. The study intervention will be administered intramuscularly by injecting a 0.5-mL dose from the MDV, or the entire contents of the SDV, into the deltoid muscle, preferably of the nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Study intervention administration will be performed by appropriately designated study staff at the investigator site.

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

Administration of study interventions will be performed by an appropriately qualified, 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.

Study intervention administration details will be recorded on the CRF.

### 6.1.2. Medical Devices

1. The manufactured medical devices provided for use in this study are a vial adaptor and PFS.

   **Note:** The vial adapter is being deployed for the reconstitution diluent for the study intervention, RSVpreF without 2-PE (SDV) only. The study intervention supplies are provided in a kit that contains the study intervention (RSVpreF 120 µg lyophilized powder in a vial), a PFS containing sterile water, and a vial adapter.

2. Instructions for medical device use are provided in the IPM.

3. Medical device deficiencies, including those resulting from malfunctions of the device, must be detected, documented, and reported by the study personnel throughout the study.

4. All medical device deficiencies (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (Section 8.4.9) and appropriately managed by the sponsor.

## 6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. 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 temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions, 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. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the IPM, package insert, or equivalent for storage conditions of the study intervention once reconstituted.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. 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.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

#### 6.2.1. Preparation and Dispensing

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention 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. A second staff member will verify the dispensing.

### 6.3. Assignment to Study Intervention

Allocation of participants to vaccine groups (randomization) will proceed through the use of an IRT system. The site will utilize the IRT system to assign the DU or container number(s) prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required.

Study intervention will be dispensed and administered at Visit 1 as summarized in the SoA.

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

### 6.4. Blinding

This is an open-label study.

#### 6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

### 6.4.2. Blinding of Site Personnel

This is an open-label study, and all site personnel including the investigator and investigator staff, and staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded.

### 6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention.

As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment and supporting clinical development.

## 6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

## 6.6. Dose Modification

Dose modification is not applicable to this protocol.

## 6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

## 6.8. Treatment of Overdose

For this study, any dose of RSVpreF greater than 1 dose of RSVpreF 120 µg within a 24-hour time period will be considered an overdose. 1 dose of study intervention is either a 0.5-mL dose from the MDV, or the entire contents of the SDV.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

### 6.9. Prior and Concomitant Therapy

#### 6.9.1. Recording Nonstudy Vaccinations and Concomitant Medications

The following concomitant medications, vaccinations, and treatments will be recorded in the CRF:

- Any vaccinations received from 28 days prior to study enrollment until the last study visit.

Participants should not enroll if they are taking or plan to take any prohibited medications and treatments listed in Section 6.9.2. However, if a participant is enrolled and required to receive prohibited medications or treatments after enrollment due to unforeseen medical reasons, record the start and stop dates, name of the prohibited product, dose, unit, route, and frequency. An AE or SAE should also be documented that reflects the medical reason why the prohibited medication or treatment was taken.

#### 6.9.2. Prohibited Concomitant Vaccinations and Treatments

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onward; however, it is anticipated that the participant would not be withdrawn from the study (unless documented as per Section 7.2). Medications should not be withheld if required for a participant's medical care.

- Receipt of any nonstudy RSV vaccine at any time prior to or during study participation.
- Investigational vaccines, drugs, or medical devices are prohibited during the course of the study.
- Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration and thereafter during the course of the study.
- Receipt of any inactivated vaccine within 14 days, or any live vaccine within 28 days, **before** study intervention administration.
- Nonstudy vaccines **may not** be given concomitantly with the study intervention or within 14 days **after** study intervention administration (Day 1 through Day 14), except if medically necessary (eg, during an outbreak or pandemic situation).
- Receipt of chronic systemic treatment with known immunosuppressant medications, other than systemic corticosteroids meeting the criteria noted below, within 60 days of administration of study intervention through conclusion of the study.

- Receipt of short-term systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment through Day 28 after administration of study intervention (Day 1).

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

- Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted prior to study intervention administration. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

### 6.9.3. Permitted Concomitant Vaccinations and Treatments

- Licensed vaccines may be given during the study starting 14 days after study intervention administration (Day 15).

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

- The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration is permitted after study intervention administration and during the participant's participation in the study.

## 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

### 7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;

- Lost to follow-up;

- Death;

- Study terminated by sponsor;

- Withdrawal due to reactogenicity;

- AEs;

- Participant request;
- Investigator request;
- Protocol deviation.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

### 7.2.1. Withdrawal of Consent

Participants who request to discontinue active study participation (eg, biological sample collection or surveillance for disease endpoints) will remain in the study for protocol-specified safety follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from specified study procedures and/or postvaccination safety follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

## 7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant 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 attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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, the participant will be considered to have withdrawn from the study.

# 8. STUDY ASSESSMENTS AND PROCEDURES

## 8.1. Administrative 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.

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 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 they have 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.

The total blood sampling volume for individual participants in this study is approximately 40 mL. The actual collection times of blood samples may change.

### 8.1.1. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. Assessments that may be performed during a telehealth visit are described in the SoA.

Study participants must be reminded to promptly notify site staff about any change in their health status.

## 8.2. Efficacy and/or Immunogenicity Assessments

### 8.2.1. Immunogenicity Assessments

Blood samples (approximately 20 mL per sample) will be collected from all participants for serum immunogenicity testing at Visit 1 (prior to study vaccination) and Visit 2 (1 month after vaccination) for antibody assessment as detailed in Section 1.3. The total volume of blood collected for antibody assessment over the course of the study will be approximately 40 mL.

Sera collected will be assayed for RSV A– and RSV B–neutralizing antibody titers. RSV A– and RSV B–neutralizing antibody titers will be determined for each serum sample and reported as the NT.

### 8.2.2. Biological Samples

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory analyst testing the samples will not know the participant's identity, study visit, or study cohort associated with the sample. 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 vaccines or vaccine-related 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 their 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.

## 8.3. Safety Assessments

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

A clinical assessment, including significant medical history, will be performed on all participants at their first visit to establish a baseline. Significant medical history and observations from any physical examination and vital sign assessments, if performed, will be documented in the CRF.

AEs and SAEs are to be collected, recorded, and reported as defined in Section 8.4.

Acute reactions within the first 30 minutes after administration of the study intervention will be assessed and documented in the CRF.

Safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever) that occur in the first 7 days or longer after administration of the study intervention. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in Section 8.3.5.2 and Section 8.3.5.3.

### 8.3.1. Physical Examinations

If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, a physical examination will be performed.

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 2) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

### 8.3.2. Vital Signs

The participant's prevaccination temperature will be measured as per usual clinical practice. Additionally, height, weight, seated blood pressure, and pulse rate will be measured prior to the participant's vaccination.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 2) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

### 8.3.3. Clinical Safety Laboratory Assessments

Clinical safety laboratory assessments will not be collected in this study.

### 8.3.4. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at Visit 1, immediately before the administration of study intervention. A negative pregnancy test result will be required prior to receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention and from the study.

### 8.3.5. Electronic Diary

All participants will be required to use an e-diary, installed on a provisioned device or as an application on a personal device, and will be asked to monitor and record prespecified local reactions and systemic events, and temperature daily for 7 days or longer following vaccination (Day 1 is the day of vaccination).

The e-diary allows recording of assessments each day, thus providing the accurate representation of the participant's experience at that time.

Data on local reactions, systemic events, and temperature recorded in 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 into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF except the following conditions:

- If a participant withdraws because of prespecified event(s) recorded in the e-diary, the event(s) should be recorded on the CRF, regardless of whether the investigator considers the event(s) to be clinically significant.

- The investigator or designee must obtain stop dates for any local reactions or systemic events ongoing at Day 7 through resolution. The stop dates should be documented in the source documents and the information entered in the CRF.

Investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate participant compliance and as part of the ongoing safety review. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 8.3.5.2 and Section 8.3.5.3. Please note that all provisioned e-diary devices must be collected per the SoA.

#### 8.3.5.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA CBER guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[22]

#### 8.3.5.2. Local Reactions

Following vaccination (where Day 1 is the day of vaccination), the participants will be asked to assess redness, swelling, and pain at the injection site, and to record the events in the e-diary or appropriate device daily, based on local practice.

Participants will be provided with a measuring device. Redness and swelling will be measured and recorded in measuring device units in the e-diary (range: 1 to 21).

**Note:** An entry in the e-diary of 21 will be used to denote measurements ≥21. Measurements will be 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 formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

A participant with severe redness, swelling, or pain at the injection site will be prompted to contact the investigator to perform an unscheduled visit to assess the reaction or may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns, as appropriate. In the event that the participant does not call, the investigator or qualified designee will contact the participant.

Only an investigator or a qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. If a participant experiences a Grade 4 local reaction, the investigator must immediately notify the sponsor. A Grade 4 reaction will be collected on the CRF.

The site staff will educate the participant regarding signs and symptoms that would prompt site contact.

If a local reaction persists beyond the end of the 7-day e-diary collection period, the participant will be requested to report that information and/or any new events that develop to the investigator, or the study staff. The investigational site staff will continue to contact the participant to assess and record the information daily until resolution unless recorded in the e-diary. The investigator will enter this additional information and the end date 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 |
| 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 or qualified designee is able to classify a participant's local reaction as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. Grade 4 local reactions will be collected on the CRF and assessed by the investigator or qualified designee.

### 8.3.5.3. Systemic Events

Following vaccination (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 events in the e-diary or appropriate device daily, based on local practice.

The events will be assessed by the participant according to the grading scale in Table 3. A participant with severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain will be prompted to contact the investigator to perform an unscheduled visit to assess the systemic event or may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns, as appropriate.

Participants will also be instructed to contact site staff if they visit the emergency room, have a medically attended visit, or are hospitalized for severe fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain within 7 days after vaccination.

Based on local practice, participants may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns, as applicable. In the event that the participant does not call, the investigator or qualified designee will contact the participant. The study staff may also contact the participant to obtain additional information on events entered into the e-diary.

Only an investigator or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. If a participant experiences a Grade 4 systemic event, the investigator must immediately notify the sponsor. Grade 4 reactions will be collected on the CRF.

If a systemic event persists beyond the end of the 7-day e-diary collection period, the participant will be requested to report that information and/or any new events that develop to the investigator, or the study staff. The investigational site staff will continue to contact the participant to assess and record the information daily until resolution unless recorded in the e-diary. The investigator will enter this additional information and the end date in the participant's source notes and CRF.

**Table 3. Grading Scale for Systemic Events**

| | Mild<br>Grade 1 | Moderate<br>Grade 2 | Severe<br>Grade 3 | Grade 4[a] |
|---|---|---|---|---|
| Fatigue<br>(= tiredness in diaries) | Does not interfere with activity | Some interference with activity | Prevents daily routine activity | Emergency room visit or hospitalization for severe fatigue |
| Headache | Does not interfere with activity | Some interference with activity | Prevents daily routine activity | Emergency room visit or hospitalization for severe headache |
| Vomiting | 1 to 2 times in 24 hours | >2 times<br>in 24 hours | Requires intravenous hydration | Emergency room visit<br>or hospitalization for severe vomiting |

**Table 3. Grading Scale for Systemic Events**

| | Mild Grade 1 | Moderate Grade 2 | Severe Grade 3 | Grade 4[a] |
|---|---|---|---|---|
| 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 or qualified designee is able to classify a participant's systemic event as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. Grade 4 systemic events will be collected on the CRF and assessed by the investigator or qualified designee.

### 8.3.5.4. Fever

A digital thermometer will be given to the participant with instructions on how to measure oral temperature at home. Temperature will be collected for 7 days or longer for ongoing events following vaccination (where Day 1 is the day of vaccination).

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, where possible.

In the event of a fever on the last day the e-diary was completed, temperature will be measured daily until fever has resolved (1 day of temperature <38.0°C [<100.4°F]) in order to collect a stop date. The investigator will enter this additional information in the participant's source notes and CRF.

A participant with a fever >38.9°C (>102.0°F) will be prompted to contact the investigator. Based on local practice in certain countries/locales, participants may be referred to the appropriate healthcare facility at the discretion of the study staff if there are any concerns, as applicable. In the event that the participant does not call, the investigator or a qualified designee will contact the participant. The investigator or qualified designee will assess the fever and perform an unscheduled visit as appropriate.

Only an investigator or qualified designee is able to classify a participant's fever as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. Grade 4 fevers will be collected on the CRF and assessed by the investigator.

Temperature will be measured and recorded to 1 decimal place and then categorized during analysis as mild, moderate, or severe, based on the intensity grading scale provided in Table 4.

**Table 4. Ranges for Fever**

| | Mild Grade 1 | Moderate Grade 2 | Severe Grade 3 | Grade 4[a] |
|---|---|---|---|---|
| **Fever** | ≥38.0°C-38.4°C (100.4°F-101.1°F) | >38.4°C-38.9°C (101.2°F-102.0°F) | >38.9°C-40.0°C (102.1°F-104.0°F) | >40.0°C (>104.0°F) |

a. Only an investigator or qualified designee is able to classify participant's fever as Grade 4, after clinical evaluation of the participant, documentation from another medically qualified source (eg, emergency room or hospital record), or telephone contact with the participant. Grade 4 fevers will be collected on the CRF and assessed by the investigator or qualified designee.

## 8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 2.

The definitions of device-related safety events (ADEs and SADEs) can be found in Sections 10.5.1 and 10.5.2. Device deficiencies are covered in Section 10.5.3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

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 the event meets the criteria for classification as an SAE or caused the participant to discontinue the study (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

### 8.4.1. 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 study intervention), through and including Visit 2 (1 month after study vaccination).

In this study, the investigator and site staff will ensure the active elicitation and collection of safety events as detailed below:

- The active collection period for nonserious AEs begins once informed consent has been provided and continues through and including Visit 2.
- The active collection period for AESIs and SAEs begins once informed consent has been provided until the participant completes the study.
- AEs occurring up to 48 hours after blood draws that are related to study procedures must be reported in the CRF.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the PSSA.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer via PSSA.

#### 8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the PSSA immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

#### 8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

### 8.4.2. 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 Section 10.2.

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.

### 8.4.3. Follow-Up of AEs and SAEs

After the initial AE or 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 provided in Section 10.2.

### 8.4.4. 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 toward 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 SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

### 8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

#### 8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant the investigator must report this information to Pfizer Safety using the PSSA and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until the end of the study.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the PSSA and an EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

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 report. 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. 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 or a terminated fetus) 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 including miscarriage and missed abortion should be reported as an SAE;

- 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 study intervention.

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.

#### 8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported via PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

#### 8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness via PSSA, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

### 8.4.6. Cardiovascular and Death Events

Not applicable.

### 8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

### 8.4.8. Adverse Events of Special Interest

The active collection period for AESIs begins once informed consent has been provided until the participant completes the study.

The following events are considered AESIs:

- Diagnosis of Guillain-Barré syndrome
- Diagnosis of acute polyneuropathy without an underlying etiology
- Diagnosis of atrial fibrillation
- Preterm delivery (delivery at <37 0/7 weeks' gestation)
- Diagnosis of hypertensive disorder of pregnancy

Details of the AESIs listed above are further defined in the investigator site file.

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported via PSSA.

#### 8.4.8.1. Lack of Efficacy

This section is not applicable, as efficacy is not an outcome in this study.

### 8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.5.

**Note:** AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Section 8.4.1 through Section 8.4.4 and Section 10.2 of the protocol.

#### 8.4.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

Refer to Section 10.5.4 for instructions for documenting and reporting medical device deficiencies.

#### 8.4.9.2. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

**Note:** There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

### 8.4.10. Vaccination Errors

Vaccination errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Vaccination errors are recorded and reported as follows:

| Recorded on the Medication Error Page of the CRF | Recorded on the Adverse Event Page of the CRF | Reported on the PSSA to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| All (regardless of whether associated with an AE) | Any AE or SAE associated with the vaccination error | Only if associated with an SAE |

Vaccination errors include:

- Vaccination errors involving participant exposure to the study intervention;
- Potential vaccination errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Whether or not the vaccination error is accompanied by an AE, as determined by the investigator, such vaccination errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a vaccination dosing error, the sponsor should be notified within 24 hours. Vaccination errors should be reported to Pfizer Safety within 24 hours via PSSA **only when associated with an SAE.**

### 8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

### 8.6. Genetics

#### 8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

### 8.7. Biomarkers

Biomarkers are not evaluated in this study.

### 8.8. Immunogenicity Assessments

Immunogenicity assessments are described in Section 8.2.

### 8.9. Health Economics

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

## 8.10. Study Procedures

### 8.10.1. Visit 1 – Vaccination (Clinic, 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 their 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 and **after** signing informed consent.

- Assign a participant number using the IRT system.
- Obtain the participant's demography (including age, sex, race, and ethnicity). The age will be collected to critically evaluate the immune response and safety profile by age.
- Obtain and record any medical history of clinical significance.
- Measure the participant's weight and height, seated blood pressure, and pulse rate.
- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any positive findings in the source documents and, if significant, record such findings on the medical history CRF.
- Prior to vaccination, perform a urine pregnancy test on WOCBP as described in Section 8.3.4. Record the result in the source documents. A negative pregnancy test result will be required prior to the participant's receiving the study intervention.
- Verify understanding of and compliance with protocol requirements for contraception as described in Section 5.3.1.
- Record nonstudy vaccinations given up to 28 days prior to study intervention administration, in source documents and in the CRF, if applicable. (Refer to Section 6.9 for acceptable concomitant vaccines and prohibited vaccines.)
- Obtain details of prohibited medications and treatments. See Section 6.9.
- Ensure and document that all the inclusion criteria and none of the exclusion criteria are met.

- Measure and record the participant's prevaccination body temperature using a method according to routine local practice (°C).
- Ensure that the participant meets none of the temporary delay criteria as described in Section 5.5.
- Prior to vaccination, obtain the participant's randomization number and study intervention allocation using the IRT system. Refer to the IRT manual for further instructions on this process. A site staff member will prepare the study intervention according to the IPM.
- Collect approximately 20 mL of blood prior to study intervention administration.
- Site staff member(s) will administer the study intervention into the deltoid muscle of the (preferably) nondominant arm, unless medically contraindicated, in which case the injection may be administered in the dominant arm. Please refer to the IPM for further instructions on this procedure (see Section 6.1.1).
- Site staff will observe the participant for 30 minutes after administration of the study intervention for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the CRF, and via PSSA, as applicable.
- Provide the participant with a measuring device to measure injection site reactions and a digital thermometer and provide instructions on their use.
- Explain the e-diary technologies available for this study and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device, if required. Provide instructions on e-diary completion and ask the participant to complete the e-diary from Day 1 to Day 7 or longer until any symptoms that are ongoing are resolved, 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 through Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required (see Section 8.3.5):
  - Redness and/or swelling at the injection site measuring >20 measuring device units (>10 cm);
  - Severe injection site pain (causes limitation of limb movement);
  - Fever >38.9°C (>102.0°F);
  - Any severe systemic event.

- Remind participants that the study staff may contact them to obtain additional information on symptoms entered into the e-diary until they resolve.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or medical event (eg, emergency room visit, a medically attended visit, or hospitalization) occurs to the participant.
- Provide the participant with the Pfizer study information card.
- Remind the participant to inform the study staff of any AEs, AESIs, and SAEs that occur for the duration of the study.
- Remind the participant to bring the completed e-diary to the next visit (if applicable).
- Schedule an appointment for the participant to return for the next study visit.
- The investigator or an authorized designee completes the CRF and the source documents and updates the study intervention accountability records.
- The investigator or an appropriately qualified designee reviews the e-diary data online following study intervention administration to evaluate participant compliance and as part of the ongoing safety review.

### 8.10.2. Visit 2 – 1-Month Follow-Up Visit (Clinic, 28 to 35 Days After Vaccination)

- Ensure and document that the participant continues to be eligible for the study and meets none of the participant withdrawal criteria in Section 7.2.
- Record nonstudy vaccinations since the last visit in the source documents and in the CRF, if applicable, as described in Section 6.9.3.
- Review the participant's e-diary data and record assessment in the CRF. Assess compliance and collect stop dates for any symptoms ongoing on the last day of e-diary collection period after study intervention administration. Document in the CRF.
- Collect the sponsor-provisioned e-diary/assist the participant with removing the e-diary study application from her personal device.
- Ensure that all data have been transferred before deactivating the e-diary or deleting the application.
- Remind participants that the study staff may contact them to obtain additional information on events entered into the e-diary until they resolve.

- Determine if any AEs (including nonserious AEs, AESIs, and SAEs) have occurred since the previous visit, follow up on any previously reported events to determine the outcome (ie, record stop dates or report as ongoing), and record such AEs as described in Section 8.4.1.

- Record details of any nonstudy vaccinations and prohibited concomitant medications and treatments as described in Section 6.9.1 and Section 6.9.2.

- Collect approximately 20 mL of blood for antibody assessment.

- The investigator or an authorized designee completes the CRF and the source documents.

### 8.10.3. Visit 3 – End-of-Study Visit (Telephone, 42 to 49 Days After Vaccination)

- Determine if any AESIs or SAEs have occurred since the previous visit, follow up on any previously reported events to determine the outcome (ie, record stop dates or report as ongoing), and record such events in the CRF.

- Record details of any nonstudy vaccinations and prohibited concomitant medications and treatments as described in Section 6.9.1 and Section 6.9.2.

### 8.10.4. Unscheduled Reactogenicity Visit

If a severe local reaction (Section 8.3.5.2), systemic event (Section 8.3.5.3), or fever (Section 8.3.5.4) is reported in the reactogenicity e-diary, contact **must** occur between the participant and the investigator, or a medically qualified member of the study site staff to ascertain further details and determine whether a site visit is clinically indicated. A site visit or referral to a healthcare facility 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 or appropriate designee determines that the visit is not required, or

- The investigator or appropriate designee confirmed severe reactogenicity assessment via medical records and/or telehealth assessment.

  **Note:** All contact must be recorded in the participant's source notes and in the CRF.

Any ongoing reactions must be assessed until resolved prior to or 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 or healthcare facility, who will:

- Measure temperature.
- Measure the participant's heart rate.
- Measure the participant's blood pressure (seated).
- Measure the minimum and maximum diameters of redness (if present) on the arm in which the study intervention was administered.
- Measure the minimum and maximum diameters of swelling (if present) on the arm in which the study intervention was administered.
- Assess if necrosis is present at the injection site on the arm in which the study intervention was administered.
- Assess if any exfoliative dermatitis is present.
- Assess any injection site pain that is present in the arm in which the study intervention was administered in accordance with the reactogenicity grading scale provided in Section 8.3.5.2.
- 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 8.3.5.3.
- Ask the participant if she attended an emergency room visit, had a medically attended visit, or was hospitalized.
- For severe pain at the injection site resulting in an emergency room visit or hospitalization, severe systemic events associated with an emergency room visit or hospitalization, any necrosis on the arm in which the study intervention was administered, or exfoliative dermatitis, the investigator or qualified designee must assess these events.
- Record AEs, AESIs, and SAEs as described in Section 8.4.
- Complete the participant's source documents.
- The investigator or an authorized designee will complete the CRFs.
- The study staff may contact the participant to obtain additional information on events entered into the e-diary, as appropriate.

# 9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor and finalized before database lock. 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. Statistical Hypothesis

Hypothesis testing will be used to assess the primary objectives of NI of the immune responses for RSV A and RSV B of the MDV RSVpreF group to the SDV RSVpreF group.

For the primary objective, the null hypotheses ($H_0$) for both RSV A and RSV B are:

RSV A: $H_{0A}: \ln(\mu_{MDV}) - \ln(\mu_{SDV}) \leq -\ln(1.5)$,

RSV B: $H_{0B}: \ln(\mu_{MDV}) - \ln(\mu_{SDV}) \leq -\ln(1.5)$,

where $\ln(\mu_{MDV})$ is the mean of natural logarithm–transformed antibody concentration at 1 month after vaccination from participants in the MDV RSVpreF group, and $\ln(\mu_{SDV})$ is the mean of natural logarithm–transformed antibody concentration at 1 month after vaccination from participants in the SDV RSVpreF group. 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 NI of RSVpreF of the MDV group with respect to the SDV group will be evaluated at 1 month after vaccination for RSV A and RSV B NTs. The primary objective of NI will be met if

- The lower bounds of the 2-sided 95% CI for the GMT ratio (MDV group divided by SDV group) are greater than the predefined limit of 0.67 (NI margin of 1.5-fold) for both RSV A and RSV B NTs.

### 9.1.1. Estimands

#### 9.1.1.1. Primary Estimand/Coprimary Estimands

##### 9.1.1.1.1. Immunogenicity

The estimand is defined by the following attributes:

Population: Participants receiving 1 dose of study intervention and in compliance with the key protocol criteria (evaluable participants).

Endpoints:

- Functional antibody levels estimated by the GMT for RSV A and RSV B serum NTs before vaccination and at 1 month after vaccination.

- GMR, estimated by the ratio of the GMTs for RSV A and RSV B serum NTs of the MDV group to the SDV group before vaccination and at 1 month after vaccination.

Treatment condition: The randomized MDV group or SDV group.

Intercurrent events: The following intercurrent events could impact the interpretation or the measurement of the immune response: 1) The participants with major protocol violation who received a prohibited vaccine or 2) treatment that may alter the immune response and subsequently impact the vaccine protection. The immunogenicity data after intercurrent events will be excluded (hypothetical strategy). Major protocol violations will be determined by clinical review. Missing serology results will not be imputed, as MCAR is assumed.

Population-level summary: GMR of the GMTs for RSV A and RSV B serum NTs of the MDV group to the SDV group.

#### 9.1.1.1.2. Safety

The estimand is defined by the following attributes:

Population: Participants receiving 1 dose of study intervention.

Endpoints:

- Local reactions within 7 days after vaccination.
- Systemic events within 7 days after vaccination.
- The percentage of participants having AEs through 1 month after vaccination.
- The percentage of participants reporting SAEs throughout the study.

Treatment condition: The administered MDV group or SDV group.

Intercurrent events: There are no intercurrent events to be considered. All data collected after discontinuation or major protocol deviation would be included. Missing e-diary data will not be imputed; missing AE dates and missing AE intensity data will be handled according to Pfizer safety rules.

Population-level summary: The percentage of participants reporting local reactions, systemic events, AEs, and SAEs in each group.

### 9.1.1.2. Secondary Estimands

#### 9.1.1.2.1. Immunogenicity

The estimand is defined by the following attributes:

Population: Participants receiving 1 dose of study intervention and in compliance with the key protocol criteria (evaluable immunogenicity participants).

Endpoint: Seroresponse rates, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the prevaccination titer; or ≥4 times the LLOQ if the prevaccination titer is below the LLOQ.

Treatment condition: The randomized MDV group or SDV group.

Intercurrent events: The intercurrent events listed in Section 9.1.1.1.1 apply.
The immunogenicity data after intercurrent events will be excluded (hypothetical strategy). Major protocol violations will be determined by clinical review. Missing serology results will not be imputed, as MCAR is assumed.

Population-level summary: Seroresponse rates by vaccine group.

### 9.1.2. Multiplicity Adjustment

No multiplicity adjustment is needed for this study, as both RSV A and RSV B need to meet the NI criteria.

## 9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

| Participant Analysis Set | Description |
|---|---|
| Enrolled | All participants who sign the ICD. |
| Randomized | All participants who are assigned a randomization number in the IRT system. |
| Safety | All participants who receive the study intervention. |

| Defined Analysis Set | Description |
|---|---|
| Evaluable immunogenicity | All participants who are eligible, receive the study intervention to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations. |
| mITT immunogenicity | All randomized participants who receive the study intervention and have at least 1 valid and determinate assay result for the proposed analysis. |

## 9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe 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, secondary, and exploratory endpoints.

### 9.3.1. General Considerations

In general, the study data will be summarized by study intervention group. CIs for all endpoints in the statistical analysis will be presented as 2-sided at the 95% level.

For all the immunogenicity endpoints, the analysis will be primarily based on the evaluable immunogenicity population. An additional analysis will be performed based on the mITT population if there is a large enough difference in the number of participants included between the mITT and the evaluable immunogenicity populations. Participants will be summarized according to the study intervention group to which they were randomized. Missing laboratory results will not be imputed.

The safety analyses are based on the safety population. Participants will be summarized according to the study interventions they received.

### 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

#### 9.3.2.1. Immunogenicity

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary – immunogenicity | • GMT for RSV A and RSV B serum NTs and the associated 2-sided 95% CIs will be provided, by study intervention, before vaccination and at 1 month after vaccination.<br>• GMR, estimated by the ratio of the GMTs for RSV A and RSV B serum NTs of the MDV group to the SDV group and the associated 2-sided 95% CIs will be provided, by study intervention, before vaccination and at 1 month after vaccination.<br>• For GMT analysis, a titer reported as < LLOQ will be converted to a value of ½ LLOQ.<br>• The analysis is based on the evaluable population. An additional analysis will be performed based on the mITT population if there is a large enough difference in the number of participants included between the mITT and the evaluable immunogenicity populations. Participants will be summarized according to the study intervention group to which they were randomized.<br>• Missing serology data will not be imputed. |

#### 9.3.2.2. Safety

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary – safety | • Point estimates and the associated exact 2-sided 95% CIs will be calculated using the Clopper-Pearson method for the proportion of participants reporting each event (local reactions, systemic events, AEs, and SAEs) for each study intervention.<br>• AEs and SAEs will be categorized according to MedDRA terms.<br>• A 3-tier 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 RSVpreF in the MDV group and RSVpreF in the SDV group will be calculated using the test statistic proposed by Miettinen and Nurminen,[25] 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. A MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants with the AE term in at least 1 vaccine group. Descriptive summary statistics (counts and percentages) will be provided for Tier 3 events for each vaccine group.<br>• The safety analyses are based on the safety population. Participants will be summarized by the vaccine group they actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE intensity will be addressed using the Pfizer safety rules. |

### 9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

| Endpoint | Statistical Analysis Methods |
|---|---|
| Secondary – immunogenicity | • Seroresponse rates, by vaccine group, defined as a ≥4-fold rise in serum NTs at 1 month after vaccination compared to the prevaccination titer; or ≥4 times the LLOQ if the prevaccination titer is below the LLOQ.<br>• Exact 2-sided 95% CIs for the percentages (seroresponders) will be provided using the Clopper-Pearson method.<br>• The analysis is based on the evaluable immunogenicity population. An additional analysis will be performed based on the mITT population if there is a large enough difference in the number of participants included between the mITT and the evaluable immunogenicity populations. Participants will be summarized according to the study intervention group to which they were randomized.<br>• Missing serology data will not be imputed. |

### 9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

| Endpoint | Statistical Analysis Methods |
|---|---|
| Exploratory – immunogenicity | • GMC for RSV A and RSV B prefusion F–binding IgG and the associated 2-sided 95% CIs will be provided, by study intervention, before vaccination and at 1 month after vaccination.<br>• For GMC analysis, an IgG level reported as < LLOQ will be converted to a value of ½ LLOQ.<br>• The analysis is based on the evaluable population. An additional analysis will be performed based on the mITT population if there is a large enough difference in the number of participants included between the mITT and the evaluable immunogenicity populations. Participants will be summarized according to the study intervention group to which they were randomized.<br>• Missing serology data will not be imputed. |

### 9.3.5. Other Safety Analyses

All safety analyses will be performed on the safety population.

## 9.4. Interim Analyses

No interim analysis will be conducted for this study.

## 9.5. Sample Size Determination

The study sample size is based on the evaluation of NI of RSVpreF in the MDV group to RSVpreF in the SDV group on the primary endpoint. NI will be evaluated using a 1.5-fold margin as the criterion. With the assumption of SD (ln scale) from the historical study, Table 5 presents the power to demonstrate NI for both RSV A and RSV B. The overall power to demonstrate NI for both RSV A and RSV B is 90.0%.

Assuming a nonevaluable rate of 10%, the study will randomize approximately 452 participants to achieve 203 evaluable participants in each group.

**Table 5. Power to Show Noninferiority of RSVpreF in the MDV Group to the SDV Group**

| Endpoint | ln(SD) | Assumed GMT Ratio | NI Margin | N Evaluable/Group | | Power |
|---|---|---|---|---|---|---|
| | | | | MDV | SDV | |
| RSV A | 1.09 | 1 | 1.5-fold | 203 | 203 | 96.2% |
| RSV B | 1.17 | 1 | 1.5-fold | 203 | 203 | 93.6% |
| Power to show NI for both RSV A and RSV B | | | | | | 90.0% |

# 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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European MDR 2017/745 for clinical device research, 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 study intervention, 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 the ICH GCP guidelines 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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each 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 their 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 their 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 their right to access and correct their personal data and to withdraw consent for the processing of their 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 on which 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 IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

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

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

#### 10.1.3.1. Electronic Consent

Participants may be able to experience the informed consent process by electronic means (eConsent). The eConsent process includes an electronic presentation of the informed consent document (eICD), clinical trial educational components (as applicable), and electronic signatures (if allowed by local regulations). The use of eConsent does not replace or alter the ICD content or informed consent process as described above. The eConsent process complies with applicable regulations and sponsor policies to ensure reliability and data privacy.

### 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 will 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 participants 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 their actual identity and medical record ID. 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

### 10.1.5. Committees Structure

#### 10.1.5.1. Data Monitoring Committee

This study will not use an EDMC.

### 10.1.6. 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 EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its 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 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. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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.

### 10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and 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, including definition of study-critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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.

### 10.1.8. 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 eCRF that are 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 a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the data management plan, which is maintained by the sponsor.

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

The sponsor or designee will perform monitoring 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 guidelines, and all applicable regulatory requirements.

### 10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

### 10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

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, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. 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 sponsor or designee/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 the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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.

### 10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer 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-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

### 10.1.12. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the investigator site file or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

## 10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

### 10.2.1. 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.<br><br>• 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, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE:<br><br>  • Is associated with accompanying symptoms.<br><br>  • Requires additional diagnostic testing or medical/surgical intervention.<br><br>  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.<br><br>• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.<br><br>• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.<br><br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br><br>• 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 or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. |

| **Events NOT Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.<br><br>• 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.<br><br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br><br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br><br>• 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. |

### 10.2.2. Definition of an SAE

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br><br>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**<br><br>In general, hospitalization signifies that the participant has been admitted (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.<br><br>Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE. |

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:** |
|---|
| **d. Results in persistent or significant disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **e. Is a congenital anomaly/birth defect** |
| **f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic**<br>The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate. |
| **g. Other situations:**<br>• Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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.<br>• 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. |

### 10.2.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

**AE and SAE Recording/Reporting**

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs via PSSA to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the PSSA 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 PSSA for reporting of SAE information.

| Safety Event | Recorded on the CRF | Reported on the PSSA to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| SAE | All | All |
| Nonserious AE | All | None |
| Exposure to the study intervention under study during pregnancy or breastfeeding | All AEs or SAEs associated with EDP or EDB<br>Note: Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF | All instances of EDP are reported (whether or not there is an associated SAE)*<br>All instances of EDB are reported (whether or not there is an associated SAE)** |
| Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB) | None. Exposure to a study nonparticipant is not collected on the CRF | The exposure (whether or not there is an associated AE or SAE) must be reported*** |

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety using the PSSA and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the PSSA or Vaccine SAE Report Form.

** **EDB** is reported to Pfizer Safety using the PSSA, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the PSSA.

- When an AE or 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 or 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 PSSA/AE or SAE CRF page.

**AE and SAE Recording/Reporting**

- 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- 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 or 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:

| | | |
|---|---|---|
| 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. |

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.

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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 their 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 study intervention caused the event, then the event will be handled as "related to study intervention" 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 PSSA 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 providers.<br><br>• 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.<br><br>• New or updated information will be recorded in the originally submitted documents.<br><br>• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information. |

### 10.2.4. Reporting of SAEs

| **SAE Reporting to Pfizer Safety via an Electronic DCT** |
|---|
| • The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA).<br><br>• If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.<br><br>• The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.<br><br>• After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.<br><br>• 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 DCT 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 the Vaccine SAE Report Form** |
|---|
| • Facsimile transmission of the Vaccine SAE Report Form is the back-up method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours. In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service.<br><br>• Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames. |

## 10.3. Appendix 3: Contraceptive and Barrier Guidance

### 10.3.1. Female Participant Reproductive Inclusion Criteria

The criteria below are part of inclusion criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.3.3. for a complete list of contraceptive methods permitted in the study.

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 10.3.2).

  OR

- Is a WOCBP and agrees to use an acceptable contraceptive method 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.

### 10.3.2. Woman of Childbearing Potential

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

If fertility is unclear (eg, amenorrhea or oligomenorrhea) 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. Premenarchal.
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to a 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.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.3.3. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

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 WOCBP 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.

Highly Effective Methods That Are User Dependent

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

Other Effective Methods

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).

## 10.4. Appendix 4: 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 DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

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 AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili 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 T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), 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/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or 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, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the 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.

## 10.5. Appendix 5: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

**Definitions of a Medical Device Deficiency**

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.2 for the list of sponsor medical devices).

### 10.5.1. Definition of AE and ADE

| AE and ADE Definition |
|---|
| • An AE is defined in Appendix 2 (Section 10.2.1).<br><br>• An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. |

### 10.5.2. Definition of SAE, SADE, and USADE

| SAE Definition |
|---|
| • An SAE is defined in Appendix 2 (Section 10.2.2). |
| **SADE Definition** |
| • An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.<br><br>• Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate. |

| **USADE Definition** |
| --- |
| • A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is an SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file. |

### 10.5.3. Definition of Device Deficiency

| **Device Deficiency Definition** |
| --- |
| • A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer. |

### 10.5.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

| **Device Deficiency Recording** |
| --- |
| • When a device deficiency 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.<br><br>• The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice.<br><br>• If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.<br><br>• The investigator will notify the sponsor study team by any contact method within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.<br><br>• The sponsor study team will capture the required information on the Medical Device Complaint form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group. |

**Device Deficiency Recording**

- If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. All relevant details related to the role of the device in regard to the SAE must be included in the PSSA as outlined in Section 8.4.1.1 and Section 8.4.1.2.

- 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. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.

- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

**Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency**

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.

- 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.

- 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 their assessment.

**Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency**

- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have 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 their 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.

**Follow-Up of Medical Device Deficiency**

- Follow-up applies to all participants, including those who discontinue study intervention.
- 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 device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form by the sponsor study team.
- New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety using the PSSA within 24 hours of receipt of the information, according to the requirements provided in Appendix 2.

## 10.6. Appendix 6: Protocol-Specific Requirements; Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

1. Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/$mm^3$ within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

2. History of chronic HCV infection with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

3. HBeAg negative, anti-HBe positive;

4. Serum HBV DNA <2000 IU/mL;

5. Persistently normal ALT and/or AST levels;

6. In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

## 10.7. Appendix 7: Abbreviations

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

| Abbreviation | Term |
|---|---|
| 2-PE | 2-phenoxyethanol |
| ADE | adverse device effect |
| AE | adverse event |
| AESI | adverse event of special interest |
| $Al(OH)_3$ | aluminum hydroxide |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AxMP | auxiliary medicinal product |
| β-hCG | beta-human chorionic gonadotropin |
| CBER | Center for Biologics Evaluation and Research (United States) |
| CFR | Code of Federal Regulations (United States) |
| CHF | congestive heart failure |
| CI | confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CONSORT | Consolidated Standards of Reporting Trials |
| COPD | chronic obstructive pulmonary disease |
| CpG | cytosine phosphate guanine |
| CRF | case report form |
| CRO | contract research organization |
| CSR | clinical study report |
| CTIS | Clinical Trial Information System |
| DCT | data collection tool |
| DILI | drug-induced liver injury |
| DNA | deoxyribonucleic acid |
| DTwP | diphtheria, tetanus, and whole-cell pertussis vaccine |
| DU | dispensable unit |
| EC | ethics committee |
| ECG | electrocardiogram or electrocardiography |
| eCRF | electronic case report form |
| EDB | exposure during breastfeeding |
| e-diary | electronic diary |
| EDMC | external data monitoring committee |
| EDP | exposure during pregnancy |
| eICD | electronic informed consent document |
| EP | European Pharmacopoeia |
| eSAE | electronic serious adverse event |

| Abbreviation | Term |
|---|---|
| EU | European Union |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database) |
| FDA | Food and Drug Administration (United States) |
| 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 |
| HBe | hepatitis B e |
| HBeAg | hepatitis B e antigen |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HRT | hormone replacement therapy |
| IB | investigator's brochure |
| ICD | informed consent document |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ID | identification |
| IgG | immunoglobulin G |
| IMP | investigational medicinal product |
| IND | investigational new drug application |
| INR | international normalized ratio |
| IP | Internet Protocol |
| IPAL | Investigational Product Accountability Log |
| IPM | investigational product manual |
| IRB | institutional review board |
| IRT | interactive response technology |
| ISO | International Organization for Standardization |
| LFT | liver function test |
| LLOQ | lower limit of quantitation |
| LMIC | low- and middle-income country |
| LRTD | lower respiratory tract disease |
| LRTI | lower respiratory tract illness |
| LRTI-RSV | RSV-associated lower respiratory tract illness |
| MA-LRTI | medically attended lower respiratory tract illness |
| MCAR | missing completely at random |

| Abbreviation | Term |
|---|---|
| MDR | Medical Device Regulation |
| MDV | multidose vial |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent-to-treat |
| MQI | medically qualified individual |
| NI | noninferiority |
| NIMP | new investigational product |
| NT | neutralizing titer |
| PFS | prefilled syringe |
| PSSA | Pfizer's Serious Adverse Event Submission Assistant |
| PT | prothrombin time |
| QTL | quality tolerance limit |
| RNA | ribonucleic acid |
| RSV | respiratory syncytial virus |
| RSV A | respiratory syncytial virus subgroup A |
| RSV B | respiratory syncytial virus subgroup B |
| RSVpreF | respiratory syncytial virus stabilized prefusion F subunit vaccine |
| RT-PCR | reverse transcription–polymerase chain reaction |
| SADE | serious adverse device effect |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SDS | single-dose syringe |
| SDV | single-dose vial |
| SIIV | seasonal inactivated influenza vaccine |
| SmPC | summary of product characteristics |
| SoA | schedule of activities |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SUSAR | suspected unexpected serious adverse reaction |
| T bili | total bilirubin |
| Tdap | tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed |
| UADE | unanticipated adverse device effect |
| ULN | upper limit of normal |
| US | United States |
| USADE | unanticipated serious adverse device effect |
| USPI | United States prescribing information |
| VE | vaccine efficacy |
| WHO | World Health Organization |
| WOCBP | woman/women of childbearing potential |

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