Protocol C4841001

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

Statistical Analysis Plan
(SAP)

Version: 1

Date: 19 Mar 2024

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 19 Mar 2024	Protocol Amendment 1 26 Feb 2024	N/A	N/A

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C4841001. A brief description of the study design and study objectives is given below. Subsequent sections describe analysis populations and give the definitions of the endpoints, followed by details of statistical reporting. A list of tables, listings, and figures; mockup shells; and programming rules are prepared separately based on the methods described in this document.

2.1. Modifications to the Analysis Plan Described in the Protocol

This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.2. Study 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): • 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.

Objectives	Endpoints	Estimands
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). • Systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain). • AEs. • SAEs.	In participants receiving the study intervention: • The proportion of participants reporting local reactions within 7 days following study intervention administration. • The proportion of participants reporting systemic events within 7 days following study intervention administration. • The proportion of participants reporting AEs through 1 month following study intervention administration. • 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): • 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.

2.2.1. Primary Estimand(s)

2.2.1.1. Primary Immunogenicity Estimand

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 event could impact the interpretation or the measurement of the immune response: The participant's having major protocol violations (eg, receiving a prohibited vaccine or treatment) that may alter the immune response and subsequently impact the vaccine protection.

The immunogenicity data after intercurrent events will be excluded (hypothetical strategy). The intercurrent events will be determined by clinical review of major protocol violations.

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.

2.2.1.2. Primary Safety Estimand

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.

2.2.2. Secondary Estimand(s)

2.2.2.1. Secondary Immunogenicity Estimand

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).

Endpoints: 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 following intercurrent event could impact the interpretation or the measurement of the immune response: The participant's having major protocol violations (eg, receiving a prohibited vaccine or treatment) that may alter the immune response and subsequently impact the vaccine protection.

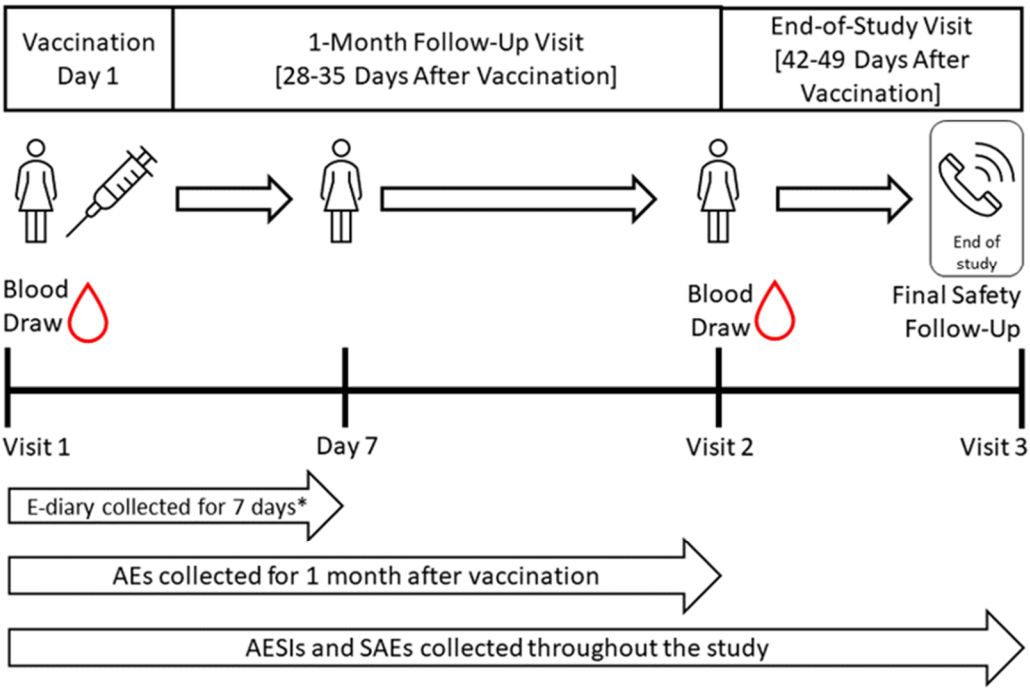
The immunogenicity data after intercurrent events will be excluded (hypothetical strategy). The intercurrent events will be determined by clinical review of major protocol violations.

Missing serology results will not be imputed, as MCAR is assumed.

Population-level summary: Seroresponse rates by vaccine group.

2.3. Study Design

This is a Phase 3, randomized (1:1), open-label study to evaluate the safety, tolerability, and immunogenicity of RSVpreF with 2-PE 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 in the study within the US. The total duration for each participant will be approximately 6 weeks.



**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.*

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

3.1.1. Primary Immunogenicity 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.

3.1.2. Primary Safety 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.

3.2. Secondary Endpoint(s)

- 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.

3.3. Other Safety Endpoint(s)

3.3.1. Adverse Events

AEs will be captured and reported in accordance with Pfizer reporting standards.

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 2 (a minimum of 28 calendar days after study intervention administration).

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 and continues 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.

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

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF and will be categorized according to the current version of MedDRA at the time of reporting.

An immediate AE is defined as any AE that occurs within the first 30 minutes after study intervention administration.

An AESI is to be recorded as an AE or SAE on the CRF. The AESI flag is captured in the CRF.

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.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.3.1).

- Tier 1 events: These are prespecified events of clinical importance, and they are maintained in a list in the product's Safety Review Plan. The AESIs are considered Tier 1 events for RSVpreF and will be analyzed for the entire study period.
- Tier 2 events: These are events that are not Tier 1 but are "common". A MedDRA PT 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.
- Tier 3 events: These are events that are neither Tier 1 nor Tier 2 events.

3.3.2. Reactogenicity Data

Reactogenicity data are solicited AEs collected using the e-diary, during Days 1 through 7, starting on the day of vaccination (Day 1). For any missed response in the e-diary (including no e-diary data), participants will be asked by the investigator at the site visit to recall any reactogenicity via the PARREACT CRF page. The reactogenicity data will include local reactions (redness, swelling, and pain at the injection site) and systemic events (fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, and joint pain).

3.3.2.1. Local Reactions

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

Presence of Local Reactions (Proportion of Participants Reporting)

Participants will be provided with a measuring device. Redness and swelling will be measured and recorded in measuring device units in the e-diary or on the PARREACT CRF page (range: 1 to 21). **Note:** An entry of 21 in the e-diary or on the PARREACT CRF page 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 4. 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 4.

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.

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 it has been recorded in the e-diary. The investigator will enter this additional information and the end date in the participant's source notes and on the CRF.

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

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

= "Yes," if the reaction is recorded as "yes" for redness or swelling with a diameter of >2.0 cm or "mild," "moderate," "severe," or "Grade 4" for pain at the injection site on a given day.

= "No," if the reaction is recorded as "no" or as "yes" with a diameter of ≤2.0 cm for redness or swelling or "none" for pain at the injection site on a given day.

For each local reaction, the derivation of whether the specific reaction occurred on "any day (Day 1-7)" will be made. The derivation of this variable is given in Table 2.

Table 2. Derived Variables for Each Local Reaction

Variable[a]	Yes (1)	No (0)	Missing (.)
Any day (Day 1-7)	The reaction is reported as "yes" with a diameter of >2.0 cm for redness/swelling or "yes" for pain on any day from Day 1 through Day 7.	The reaction is reported as "no" (or "yes" with a diameter ≤2.0 cm for redness/swelling) on all 7 days or as a combination of "no" and missing on all 7 days.	The reaction is reported as missing on all 7 days.

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

For "any local reaction" on any day, a similar definition can be applied as given in Table 3.

Table 3. Derived Variables for Any Local Reaction

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

Grading Scale for Local Reactions

The grading of local reactions is listed below in Table 4.

Table 4. 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.

Maximum Severity for Local Reactions

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

= "Missing," if values are missing for all days from Day 1 through Day 7.

= 0, if all reactions are reported as "no" or a combination of missing and "no" for all days from Day 1 through Day 7.

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

If the local reaction is captured in more than 1 data source, eg, the e-diary and the PARREACT CRF page, the highest grade across all sources will be used in the summary.

Duration of Each Local Reaction

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

Onset of Local Reaction

The onset day of each local reaction will be derived.

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

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

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

3.3.2.2. 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 or the PARREACT CRF page for missed diary, based on local practice. The events will be assessed by the participant according to the grading scale in Table 5. If the systemic event is captured in more than 1 data source, eg, the e-diary and the PARREACT CRF page, the highest grade across all sources will be used in the summary.

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 it has been recorded in the e-diary. The investigator will enter this additional information and the end date in the participant's source notes and on the CRF.

Table 5. Grading Scale for Systemic Events

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

a. Only an investigator 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.

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

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.

Table 6. 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.

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

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

= "Yes," if a temperature ≥38.0°C for fever or "mild," "moderate," "severe," or "Grade 4" for the remaining events is reported on a given day.

= "No," if a temperature <38.0°C for fever or "none" for the remaining events is reported on a given day.

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

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

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 3.3.2.1). "Any systemic event" includes any fever, fatigue, headache, vomiting, nausea, diarrhea, muscle pain, or joint pain.

3.3.3. Vital Sign Data

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.

3.4. Other Endpoint(s) (Exploratory Endpoint[s])

3.4.1. Exploratory Immunogenicity Endpoint

- GMCs for RSV A and RSV B prefusion F–binding IgG before vaccination and 1 month after vaccination.

3.5. Baseline Variables

Day 1 is defined as the day of vaccination. Measurements or samples collected prior to vaccination on Day 1 are considered the baseline data for the assessments.

Demographic variables, including age, sex, ethnicity, and race, will be collected.

A clinical assessment, including significant medical history, will be performed on all participants at their first visit to establish a baseline. Medical history of clinical significance will be collected and categorized according to the current version of MedDRA at the time of reporting.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Participant Analysis Set	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to study intervention	All participants who are assigned a randomization number in the IRT system.
Evaluable immunogenicity	All participants who: • are eligible; • receive the study intervention to which they are randomized; • have blood drawn for assay testing within the specified time frame (27 to 42 days after vaccination) for 1 month after vaccination; • have at least 1 valid and determinate assay result at the 1-month follow-up visit; • and have no major protocol violations. Participants will be analyzed according to the study intervention as randomized.
mITT	All randomized participants who receive study intervention and have at least 1 valid and determinate assay result after vaccination. Participants will be analyzed according to the study intervention as randomized.
Safety	All randomized participants who receive study intervention. Participants will be analyzed according to the study intervention they actually received. A randomized participant who did not receive study intervention will be excluded from the safety analyses.

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

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

Hypothesis testing will be used to assess the primary objective of noninferiority of the immune responses for RSV A and RSV B induced by the MDV RSVpreF group to those induced by 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 RSVpreF MDV group, and $\ln(\mu_{SDV})$ is the mean of natural logarithm–transformed antibody concentration at 1 month after vaccination from participants in the RSVpreF SDV group. The antibody titer data will be logarithmically transformed for the analysis of GMT ratios along with 95% CIs, and results will be presented on the original scale.

The noninferiority of the MDV RSVpreF group with respect to the SDV RSVpreF group will be evaluated at 1 month after vaccination for RSV A– and RSV B–neutralizing antibody titers. The primary objective of noninferiority will be met if:

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

5.2. General Methods

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

All safety and immunogenicity data will be summarized by vaccine group. Immunogenicity results will be summarized according to the study intervention group to which participants are randomized. Safety results will be summarized by group based on the study intervention the participants actually received.

5.2.1. Analyses for Binary Endpoints

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

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

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

5.2.2. Analyses for Continuous Endpoints

Unless otherwise specified, the CI for the mean of a continuous variable will be constructed by the standard method based on the Student t distribution.

5.2.2.1. Geometric Mean Titers/Concentrations

Continuous immunogenicity endpoints will be logarithmically transformed for analysis.

GMT/GMC and associated 2-sided 95% CI will be calculated at each available time point for each vaccine group. 95% CI will be calculated by back transformation of the 95% CI for the mean of the logarithmically transformed assay results computed using the Student t distribution.

5.2.2.2. Geometric Mean Ratio

The GMR will be calculated as the group mean difference of logarithmically transformed antibody levels and back transformed to the original units of the MDV group to SDV group. Two (2)-sided 95% CI will also be computed by back transformation of the CIs using 2-sample Student t distribution for the mean difference of measures on the logarithmically transformed assay results.

5.2.2.3. Geometric Mean Fold Rise

The GMFR will be calculated by exponentiating the mean difference of an individual participant's logarithmically transformed titer levels (1-month postvaccination level minus prevaccination level). 95% CI will be obtained by exponentiating the limits of the 95% CI for the mean difference of the logarithmically transformed assay results using the Student t distribution.

5.2.2.4. Reverse Cumulative Distribution Curves

RCDCs for RSV A and RSV B serum NTs for a combination of available time points and vaccine groups will be generated.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

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

5.3.1.1. Reactogenicity Data

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

The reactogenicity data are collected in the e-diary, which allows participants to enter data later if for some reason they missed an earlier opportunity to do so. Additionally, for any e-diary entries that are out of the window to reenter the information in the e-diary recollection period, the data will be collected onsite via the PARREACT CRF page. Therefore, it is expected that very few e-diary entries would be missing.

5.3.2. Immunogenicity Data

For GMT/GMC analysis, a titer or IgG level reported as < LLOQ will be converted to a value of ½ LLOQ. The LLOQs applicable for each assay will be included in the final release assay data.

For calculating a fold rise, < LLOQ will be converted to ½ LLOQ for a numerator, and < LLOQ will be converted to LLOQ for a denominator when only 1 of either the numerator or denominator is < LLOQ. If both the numerator and denominator are < LLOQ, then both will be converted in the same way.

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Primary Immunogenicity Endpoint - RSV A– and RSV B–Neutralizing Antibody Titers Measured at 1 Month After Vaccination

6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Population: Evaluable immunogenicity (Section 4).
- Statistical method/test: Hypothesis testing.
- Method of handling intercurrent events (Section 2.2.1) and missing values (Section 5.3): The immunogenicity data after intercurrent events will be censored. Missing serology results will not be imputed, as MCAR is assumed.

- GMTs of RSV A and RSV B serum NTs will be summarized for each vaccine group, along with associated 2-sided 95% CIs.
- GMT of the combined RSV A/B serum NTs will be descriptively summarized for each vaccine group, along with associated 2-sided 95% CIs.
- GMRs, 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 will be calculated, along with associated 2-sided 95% CIs.
- GMFRs and associated 2-sided 95% CIs will be provided for RSV A and RSV B serum NTs from before vaccination to 1 month after vaccination for each vaccine group.
- GMFR and associated 2-sided 95% CIs will be provided for combined RSV A/B serum NTs from before vaccination to 1 month after vaccination for each vaccine group.
- Empirical RCDCs for RSV A and RSV B serum NTs for the prespecified time points and vaccine groups will be generated.
- A forest plot with GMRs and associated 95% CIs for RSV A and RSV B serum NTs will be presented.

6.1.1.2. Supplementary Analyses

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

6.1.2. Primary Safety Endpoints

6.1.2.1. Local Reactions and Systemic Events Within 7 Days After Vaccination

- Estimand strategy: Treatment policy.
- Population: Safety (Section 4).
- Statistical method/test: Descriptive summary statistics.
- Method of handling intercurrent events (Section 2.2.1) and missing values (Section 5.3): There are no intercurrent events to be considered. All data collected after discontinuation or major protocol deviation will be included. Missing data will not be imputed.
- Descriptive statistics including the proportion (%), the numerator (n) and the denominator (N) used in the proportion calculation, and the 95% CI for percentage using the Clopper-Pearson method will be presented for each vaccine group.
    - Presence or absence of any local reaction/systemic event on each day (Days 1-7) after vaccination.

- Presence or absence of any local reaction/systemic event on "any day (Day 1-7)" after vaccination.
- Maximum severity of each local reaction/systemic event on "any day (Day 1-7)" after vaccination.
- Maximum severity of any local reaction/systemic event on "any day (Day 1-7)" after vaccination.

- For each vaccine group, n, mean, median, minimum, and maximum will be presented by vaccine group for the following variables for each local reaction and each systemic event:
  - Duration of each local reaction/systemic event after vaccination.
  - Onset day of each local reaction/systemic event after vaccination.
- Bar charts with the proportions of participants for each and any local reaction and each and any systemic event throughout the 7 days will be plotted for each vaccine group. The bars will be divided into severity categories to highlight the proportions of participants by maximum severity.

6.1.2.2. AEs Within 1 Month After Vaccination

- Estimand strategy: Treatment policy.
- Population: Safety (Section 4).
- Statistical method/test: Descriptive summary statistics for Tier 3 events; difference and 95% CI between the MDV group and the SDV group for Tier 1 and Tier 2 events.
- Method of handling intercurrent events (Section 2.2.1) and missing values (Section 5.3): There are no intercurrent events to be considered. All data collected after discontinuation or major protocol deviation would be included. Missing AE dates and missing AE intensity will be handled according to Pfizer safety rules.
- For each group, the number of participants with AEs within 1 month (28 days) after vaccination (n), percentage, and 95% CI (Clopper-Pearson method)[1] will be presented for any AE, each SOC, and each PT within each SOC, by vaccine group. For AEs classified as Tier 2 events, the difference in proportions and associated 2-sided 95% CI (Miettinen and Nurminen method)[2] between the MDV group and the SDV group will be presented in the summary tables.
- To support the assessment of AEs, the following AEs will be summarized with the same analysis population for each vaccine group:
  - Immediate AEs

- Related AEs
- Severe AEs
- AESIs

6.1.2.3. SAEs Throughout the Study

- Estimand strategy: Treatment policy.
- Population: Safety (Section 4).
- Statistical method/test: Descriptive summary statistics for Tier 3 events.
- Method of handling intercurrent events (Section 2.2.1) and missing values (Section 5.3): There are no intercurrent events to be considered. All data collected after discontinuation or major protocol deviation will be included. Missing AE dates and missing AE intensity will be handled according to Pfizer safety rules.
- For each group, the number of participants with SAEs throughout the study (n), percentage, and 95% CI (Clopper-Pearson method)[1] will be presented for any event, each SOC, and each PT within each SOC, by vaccine group.
- To support the assessment of SAEs, the following SAEs will be summarized with the same analysis population for each vaccine group.
  - Related SAEs
  - Severe SAEs

6.2. Secondary Endpoint(s)

6.2.1. Secondary Immunogenicity Endpoint

6.2.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Population: Evaluable immunogenicity (Section 4).
- Statistical method/test: Hypothesis testing.
- Method of handling intercurrent events (Section 2.2.1) and missing values (Section 5.3): The immunogenicity data after intercurrent events will be censored. Missing serology results will not be imputed, as MCAR is assumed.
- 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.

6.2.1.2. Supplementary Analyses

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

6.3. Other Safety Summaries and Analysis Endpoint(s)

6.3.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs.

Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis. There will be no adjustment for multiple comparison in the analyses.

Analyses and summaries of primary AE endpoints using the 3-tier approach are described in detail in Section 6.1.2.2 and Section 6.1.2.3.

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

6.3.1.1. AESIs Throughout the Study

- Estimand strategy: Treatment policy.
- Population: Safety (Section 4).
- Statistical method/test: Difference and 95% CI between the MDV group and the SDV group.
- Method of handling intercurrent events (Section 2.2.1) and missing values (Section 5.3): There are no intercurrent events to be considered. All data collected after discontinuation or major protocol deviation will be included. Missing AE dates and missing AE intensity will be handled according to Pfizer safety rules.
- For each group, the number of participants with AESIs (defined in Section 3.3.1) throughout the study (n), percentage, and 95% CI (Clopper-Pearson method)[1] will be presented for any event, each SOC, and each PT within each SOC, by vaccine group. For AESIs, the difference in proportions and associated 2-sided 95% CI (Miettinen and Nurminen method)[2] between the MDV group and the SDV group will be presented in the summary table. In addition, the asymptotic p-values will also be presented for the difference between groups. A listing of AESIs will be generated.

6.3.2. Reactogenicity

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

In addition, participant data listings will be provided for all reactogenicity data (separate for local reactions and systemic events) as well as a listing for participants experiencing severe redness or swelling.

6.3.3. Vital Signs

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

6.4. Other Endpoint(s) (Exploratory Endpoint[s])

6.4.1. Exploratory Immunogenicity Endpoint

6.4.1.1. Main Analysis

- Estimand strategy: Hypothetical.
- Population: Evaluable immunogenicity (Section 4).
- Statistical method/test: Descriptive summary statistics.
- Method of handling intercurrent events (Section 2.2.1) and missing values (Section 5.3): The immunogenicity data after intercurrent events will be censored. Missing serology results will not be imputed, as MCAR is assumed.
- GMCs for RSV A and RSV B prefusion F–binding IgG before vaccination and 1 month after vaccination will be descriptively summarized for each vaccine group, along with associated 2-sided 95% CIs.
- GMFRs and associated 2-sided 95% CIs will be provided for RSV A and RSV B prefusion F–binding IgG from before vaccination to 1 month after vaccination for each group.
- GMRs, the ratio of the GMTs for RSV A and RSV B prefusion F–binding IgG of the MDV group to the SDV group, before vaccination and at 1 month after vaccination, may be calculated, along with associated 2-sided 95% CIs.

6.4.1.2. Supplementary Analyses

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

6.5. Subset Analyses

Not applicable.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

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

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

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

6.6.2. Study Conduct and Participant Disposition

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

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

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

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

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

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

6.6.3. Concomitant Medications and Nonstudy Vaccines

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

7. INTERIM ANALYSES

7.1. Introduction

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

7.2. Interim Analyses and Summaries

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

8. REFERENCES

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

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

Appendix 1. List of Abbreviations

Abbreviation	Term
2-PE	2-phenoxyethanol
AE	adverse event
AESI	adverse event of special interest
CI	confidence interval
CRF	case report form
e-diary	electronic diary
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
ICD	informed consent document
IgG	immunoglobulin G
IRT	interactive response technology
LLOQ	lower limit of quantitation
MCAR	missing completely at random
MDV	multidose vial
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NT	neutralizing titer
PARREACT	participant-reported reactogenicity
PT	preferred term
QNS	quantity not sufficient
RCDC	reverse cumulative distribution curve
RSV	respiratory syncytial virus
RSV A	respiratory syncytial virus subgroup A
RSV B	respiratory syncytial virus subgroup B
RSVpreF	respiratory syncytial virus stabilized prefusion F subunit vaccine
SAE	serious adverse event
SAP	statistical analysis plan
SDV	single-dose vial
SOC	system organ class
SOP	standard operating procedure
US	United States

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Signed By:	Date(GMT)	Signing Capacity
PPD	19-Mar-2024 17:11:32	Manager Approval