Protocol B5091019

A PHASE 3, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE IMMUNOGENICITY, SAFETY, AND TOLERABILITY OF 2 DOSES COMPARED TO 3 DOSES OF *CLOSTRIDIUM DIFFICILE* VACCINE IN ADULTS 50 YEARS OF AGE AND OLDER

Statistical Analysis Plan
(SAP)

Version: 2

Author: PPD

Date: 29 Sep 2020

TABLE OF CONTENTS

LIST OF TABLES

1. VERSION HISTORY

The statistical analysis plan (SAP) Version 1 for Study B5091019 is based on the protocol dated 02 May 2019. This SAP amendment (Version 2) is updated to align with some changes to the analysis as mentioned in Table 1.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not applicable	Not applicable
2	Minor updates in Section 2.2.2, Section 3.4.3, Section 3.5.2.1, Section 4.1, Section 4.2, Section 4.3, Section 5, Section 6 and Section 7.2.	• Following regulatory consultation, antibody concentration levels below the lower limit of quantitation (LLOQ) are imputed to the appropriate LLOQ value when determining seroresponse. • Clarification was added to the duration calculations for reactogenicity events, based on Food and Drug Administration (FDA) comments for the study data standardization plan. • Clarifications were added regarding the evaluable immunogenicity populations determined at Month 7 and Month 12. • Immunogenicity analysis using the modified intent-to-treat (mITT) population will be limited based on the relative size of the mITT population. • Clarification was added to identify participants to be included in specific vaccine regimens within the safety analysis population. • Clarification was added to identify individual participant data cutoff time points for inclusion in the interim analyses.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B5091019. 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. Any major deviations from the methods specified in this document and the protocol will be discussed in the clinical study report (CSR).

2.1. Study Objectives, Endpoints, and Estimands

Primary Immunogenicity Objective:

- To demonstrate the noninferiority of a 2-dose regimen of the *Clostridium difficile* vaccine compared to a 3-dose regimen of the *C difficile* vaccine at Month 7.

Primary Safety Objective:

- To evaluate the safety of *C difficile* vaccine when administered to participants in a 2-dose regimen or a 3-dose regimen by assessing local reactions and systemic events, adverse events (AEs), and serious adverse events (SAEs).

Secondary Objective:

- To demonstrate the noninferiority of a 2-dose regimen of the *C difficile* vaccine compared to a 3-dose regimen of the *C difficile* vaccine at Month 12.

CCI [redacted]

2.1.1. Primary Immunogenicity Estimands

- For each of toxin A– and toxin B–specific neutralizing antibody levels at Month 7: Adjusted geometric mean concentration (GMC) ratio, estimated by the ratio of the adjusted GMC (adjusted for baseline concentration) for the 2-dose regimen to the adjusted GMC for the 3-dose regimen, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants).

- For each of toxin A– and toxin B–specific neutralizing antibody levels at Month 7: Seroresponse difference, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants).

- Seroresponse for each of toxin A– and toxin B–specific neutralizing antibody levels: For both seronegative (baseline concentration < lower limit of quantitation [LLOQ]) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from the baseline neutralizing antibody level following vaccination.

2.1.2. Primary Safety Estimands

- In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting local reactions.

- In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting systemic events.

- In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting nonserious AEs.

- In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting SAEs.

2.1.3. Secondary Estimands

- For each of toxin A– and toxin B–specific neutralizing antibody levels at Month 12: Adjusted GMC ratio, estimated by the ratio of the adjusted GMC (adjusted for baseline concentration) for the 2-dose regimen to the adjusted GMC for the 3-dose regimen, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants).

- For each of toxin A– and toxin B–specific neutralizing antibody levels at Month 12: Seroresponse difference, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants).

- Seroresponse for each of toxin A– and toxin B–specific neutralizing antibody levels: For both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from the baseline neutralizing antibody level following vaccination.

2.2. Study Design

2.2.1. Description

This is a Phase 3, randomized, observer-blinded study to evaluate the immunogenicity, safety, and tolerability of CCI containing *C difficile* vaccine (200 μg total toxoids per dose) administered at Months 0, 1, and 6 (3-dose group) or at Months 0 and 6 (2-dose group) and 1 dose of placebo (normal saline) at Month 1 in adults 50 years of age and older.

Approximately 1960 adults, 50 years of age and older, will be randomized into 1 of 2 groups in a 1:1 ratio (2-dose *C difficile* vaccine : 3-dose *C difficile* vaccine). In order to enroll a broad representation of age groups among those 50 years of age and older, the randomization into an age cohort will be managed by the central randomization process. The targeted number of participants and the age cohorts intended to be randomized are shown in Table 2.

Table 2. Intended Number of Participants Included in the Study, by Age Category

Age Category	Minimum Number for Inclusion	Maximum Number for Inclusion
50-59 years	Not limited	200 participants
60-69 years	200	Not limited
≥70 years	200	Not limited

A participant is considered to have completed the study if he/she has completed the last scheduled procedure in the schedule of activities as shown Table 5.

2.2.2. Number of Participants

In order to meet the immunogenicity primary objective, the study sample size estimate is based upon the evaluation of noninferiority of a 2-dose regimen to a 3-dose regimen with respect to toxin A– and toxin B–specific neutralizing antibodies.

Regimen comparisons will be based on 2 primary endpoints assessed 1 month after the last dose (Month 7):

1. The GMC ratios adjusted by the baseline antibody level and corresponding 95% confidence intervals (CIs).

2. The difference in percentage of participants achieving seroresponse and the corresponding 95% CIs.

The noninferiority of a 2-dose regimen to a 3-dose regimen at 1 month after the last dose will be evaluated using a 1.5-fold noninferiority margin for the adjusted GMC ratio and a 10% noninferiority margin for the difference of seroresponse rate as noninferiority criteria.

Pfizer has developed a new assay that will be used for serology testing in this study. The new assay was used to test Study B5091009 samples retrospectively, and the standard deviation was evaluated. Therefore, the computation of the sample size for the GMC ratio is based on (1) the standard deviations (0.794 for toxin A and 1.059 for toxin B) from Study B5091009 samples tested by the new assay and (2) an assumption that the true mean difference between the 2 regimens for both toxin A– and toxin B–specific neutralizing antibody levels is no more than 0.2 on the logarithmic scale. Similarly, the reference for the computation of the sample size for the difference in seroresponse rate is based on the percentage of seroresponse (4-fold rise from baseline) observed from Study B5091009, and an assumption that the true seroresponse rate for the 2-dose regimen is no more than 3% lower than the rate for the 3-dose regimen. A sample size of 784 evaluable participants per regimen will provide a power of 96.91% to declare the noninferiority of a 2-dose regimen to a 3-dose regimen for both toxin A and toxin B in terms of the GMC ratio, 1 month after the last dose (Table 3). The sample size will also provide a power of 93.64% to declare the noninferiority of a 2-dose regimen to a 3-dose regimen for both toxin A and toxin B in terms of the difference of percentage of participants achieving seroresponse, 1 month after the last dose (Table 4). Thus, the overall power to meet the study primary immunogenicity objective is 90.7%.

Table 3. Power Analysis (Primary Immunogenicity Objective: Noninferiority for GMC Ratio)

Criteria	Neutralizing Antibody	Standard Deviation (Log Value)[a]	Assumed Observed Log GMC Difference	Number of Evaluable Participants per Regimen	Power[b]	Power to Meet NI for Both Toxins at 1 Month After Dose 3
Lower limit of 95% CI for GMC ratio (2 doses/3 doses) >0.67	Toxin A	0.794	0.2	784	99.92%	96.91%
	Toxin B	1.059	0.2	784	96.99%	

Abbreviations: GMC = geometric mean concentration; NI = noninferiority

a. Reference Study B5091009 tested by the new assay, 1 month after Dose 3.

b. At 0.05 alpha level (2-sided).

Table 4. Power Analysis (Primary Immunogenicity Objective: Noninferiority for Difference in Seroresponse)

Criteria	Neutralizing Antibody	Observed % of Seroresponse From 3-Dose Group[a]	Assumed % of Seroresponse From 2-Dose Group	Number of Evaluable Participants per Regimen	Power[b]	Power to Meet NI for Both Toxins at 1 Month After Dose 3
Lower limit of 95% CI for difference of seroresponse rate (2 doses minus 3 doses) > -10%	Toxin A	82.3%	79.3%	784	93.93%	93.64%
	Toxin B	92.4%	89.4%	784	99.7%	

Abbreviations: BLQ = below the limit of quantitation; LLOQ = lower limit of quantitation; NI = noninferiority.
Note: Seroresponse = participant achieves at least a 4-fold rise after the last vaccination (antibody concentration levels below the LLOQ or denoted as BLQ will be set to the appropriate LLOQ value).
a. Reference Study B5091009.
b. At 0.05 alpha level (2-sided).

A sufficient number of participants will be screened to achieve 1960 participants randomly assigned to investigational product and 1568 evaluable participants (assuming a maximum study nonevaluable rate of 20%), for an estimated total of 784 evaluable participants per vaccine group in order to meet the primary immunogenicity objectives.

2.2.3. Schedule of Activities

The schedule of activities table provides an overview of the protocol visits and procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed in Table 5, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 5. Schedule of Activities

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Visit Description	**Month 0 (Vax 1)**	**Month 1 (Vax 2)**	**Month 2 (Phone Contact)**	**Month 6 (Vax 3)**	**Month 7**	**Month 9**	**Month 12 (End of Study)**
Visit Window (Days)	**1**	**28-42 Days After Visit 1**	**28-42 Days After Visit 2**	**140-168 Days After Visit 2**	**28-42 Days After Visit 4**	**84-98 Days After Visit 4**	**165-195 Days After Visit 4**
Informed consent[a]	X						
Demography[a]	X						
Clinical assessment, including medical history[a]	X						
Record nonstudy vaccinations[b]	X	X	X	X	X		
Measure and record height and weight[a]	X						
Oral temperature[a]	X	X		X			

Table 5. Schedule of Activities

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Visit Description	**Month 0 (Vax 1)**	**Month 1 (Vax 2)**	**Month 2 (Phone Contact)**	**Month 6 (Vax 3)**	**Month 7**	**Month 9**	**Month 12 (End of Study)**
Visit Window (Days)	**1**	**28-42 Days After Visit 1**	**28-42 Days After Visit 2**	**140-168 Days After Visit 2**	**28-42 Days After Visit 4**	**84-98 Days After Visit 4**	**165-195 Days After Visit 4**
Urine pregnancy test (women of childbearing potential)[a]	X	X		X			
Discuss contraceptive use[b]	X	X	X	X			
Confirm eligibility[b]	X	X	X	X	X	X	
Review temporary delay criteria[a]	X	X		X			
Randomization[a]	X						
Blood draw for immunogenicity assessment[b]	20 mL			20 mL	20 mL + 40 mL[c]	20 mL[d]	20 mL[d]
Vaccination	X	X		X			
Postvaccination observation (30 minutes) and AE assessment	X	X		X			
Issue e-diary, measuring device, and thermometer and provide instructions on their use, as required	X	X		X			
Record AEs	X <----	X ----	X ----	X ---->	X	X[d]	X[d]
Record SAEs	X <----	X ----	X ----	X ----	X ----	X ---->	X
Telephone contact			X				
Participant completes e-diary	X <----	X ----		X ---->			
Review e-diary data[e]							
Collect e-diary					X		

Abbreviations: CRF = case report form; e-diary = electronic diary; Vax = vaccination; ----> = ongoing/continuous event.

a. Prior to vaccination.
b. Prior to vaccination, if at a vaccination visit.
c. Additional (optional) blood will be collected for the purposes of vaccine assay development.
d. Any AEs occurring up to 48 hours after blood draw must be recorded in the CRF.
e. E-diary data review is ongoing during participant e-diary data entry periods (7 days after each vaccination) via an internet-based portal.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTION

The primary analysis for immunogenicity and safety assessment will be performed at Visit 5 (Month 7). In addition, a secondary immunogenicity and safety assessment will be performed at Visit 7 (Month 12). For all immunogenicity assessments, baseline will be the Visit 1 (Month 0) assessment prior to the first dose of *C difficile* vaccine.

3.1. Primary Endpoints

3.1.1. Primary Immunogenicity Endpoints

- *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 7 in each regimen, expressed as adjusted GMCs, estimated by the ratio of the adjusted GMC (adjusted for baseline concentration) for the 2-dose regimen to the adjusted GMC for the 3-dose regimen.
- *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 7 in each regimen, expressed by seroresponse difference, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse. Seroresponse for each of toxin A– and toxin B–specific neutralizing antibody levels: for both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from the baseline neutralizing antibody level following vaccination.

3.1.2. Primary Safety Endpoints

- Participants reporting local reactions (pain, erythema, and induration), as self-reported in electronic diaries (e-diaries) for up to 7 days following each dose of investigational product in each regimen, expressed as percentages.
- Participants reporting systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain), as self-reported in e-diaries for up to 7 days following each dose of investigational product in each regimen, expressed as percentages.
- Participants reporting nonserious AEs from signing of the informed consent document (ICD) to 1 month after receipt of the last dose of investigational product in each regimen, expressed as percentages.
- Participants reporting SAEs from signing of the ICD to 6 months after receipt of the last dose of investigational product in each regimen, expressed as percentages.

3.2. Secondary Endpoints

- *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 12 in each regimen, expressed as adjusted GMCs, estimated by the ratio of the adjusted GMC (adjusted for baseline concentration) for the 2-dose regimen to the adjusted GMC for the 3-dose regimen.

- *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 12 in each regimen, expressed by seroresponse difference, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse. Seroresponse for each of toxin A– and toxin B–specific neutralizing antibody levels: for both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from the baseline neutralizing antibody level following vaccination.

CCI

[redacted]

3.4. Baseline Variables

3.4.1. Demographic, Physical Examination, and Medical History

Baseline demographic variables for participants are age at randomization, sex, race, and ethnicity. Age will be calculated as (date of randomization − date of birth + 1) / 365.25 and truncated to the nearest integer less than or equal to the calculated value.

A clinical assessment, including medical history, will be performed on all participants at Visit 1 to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the case report form (CRF). Medical history for the participants will be categorized according to the current version (at time of reporting) of the Medical Dictionary for Regulatory Activities (MedDRA).

3.4.2. Nonstudy Vaccines and Concomitant Medications

Participants will be asked to provide a history with the name(s) and date(s) for all vaccinations received from 28 days prior to study enrollment until Visit 5 (1 month after the third vaccination). Unless considered medically necessary, no vaccines other than investigational product should be administered within 28 days before and 28 days after each study vaccination (administered at Visits 1, 2, and 4). Exceptions to this are the seasonal influenza vaccine and pandemic influenza vaccine, which can be given at least 14 days prior to or 14 days after the administration of investigational product. Permitted concomitant medications include the following: (1) antipyretics and other pain medication; (2) medication required for treatment of preexisting stable conditions; (3) inhaled, topical, or localized injections of corticosteroids; and (4) hormonal contraceptives that meet the requirements of this study. Individual participant use of concomitant vaccines will be listed and also summarized by dose regimen. No other use of concomitant medications will be listed or summarized.

3.4.3. Baseline Serostatus

Individual participants' baseline serostatus (prior to the first vaccination) will be defined based on the LLOQ values for *C difficile* toxin A– and toxin B– specific neutralizing antibody levels as outlined below.

- Toxin A+: baseline toxin A–specific neutralizing antibody level ≥ LLOQ for toxin A-specific neutralizing antibody level
- Toxin A–: baseline toxin A–specific neutralizing antibody level < LLOQ for toxin A-specific neutralizing antibody level
- Toxin B+: baseline toxin B–specific neutralizing antibody level ≥ LLOQ for toxin B-specific neutralizing antibody level
- Toxin B–: baseline toxin B–specific neutralizing antibody level <LLOQ for toxin B-specific neutralizing antibody level

In addition, the following 4 groups will also be defined.

- Toxin A+/toxin B+: baseline serostatus is both toxin A+ and toxin B+
- Toxin A+/toxin B–: baseline serostatus is toxin A+ and toxin B–
- Toxin A–/toxin B+: baseline serostatus is toxin A– and toxin B+
- Toxin A–/toxin B–: baseline serostatus is both toxin A– and toxin B–

CCI [redacted]
CCI [redacted] For the assessments of seroresponse difference at Month 7, at Month 12, and at Month 7 and Month 12 by age group, as well as the summary of fold rise, the *C difficile* toxin A– or toxin B–specific neutralizing antibody concentration levels below the LLOQ or denoted as below the limit of quantitation (BLQ) will be set to the appropriate LLOQ value.

For GMC and GMFR analysis, the antibody levels that are below the LLOQ or denoted as BLQ will be assigned a value of 0.5 × LLOQ.

3.5. Safety Endpoints

3.5.1. Adverse Events

Safety endpoints will include Pfizer standard safety endpoints collected in the study. An AE is defined as any untoward medical occurrence and 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, whether or not considered related to the study intervention.

The time period for actively eliciting and collecting AEs and SAEs for each participant begins from the time the participant provides informed consent through and including Visit 5 (Month 7) for AEs and through and including Visit 7 (Month 12) for SAEs. In addition, any AE occurring up to 48 hours after each blood draw, ie, after Visit 6 (Month 9) and Visit 7 (Month 12), will be recorded on the CRF. For participants who are screen failures, the active collection period ends when screen failure status is determined.

Overall AEs by category (any AE, related AEs, severe AEs, SAEs, etc) will be summarized by vaccine regimen from the date of the first dose through 1 month after the last dose (ie, including Visit 5 [Month 7]) for AEs and through 6 months after the last dose (ie, including Visit 7 [Month 12]) for SAEs. AEs and SAEs will be summarized by vaccine regimen from the date of the first dose through and including Visit 5 (Month 7) for AEs and through and including Visit 7 (Month 12) for SAEs, by MedDRA term. In addition, a participant-level listing of all AEs reported from the signing of the ICD through the day before the date of vaccination will also be provided. In general, all summaries will present the number and percentage of participants experiencing at least 1 event and the number of events for each regimen, and the exact 2-sided 95% CIs calculated using the Clopper-Pearson method.

A 3-tier approach will also be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. For Tier 1 and Tier 2 AEs, the difference in the percentages and the 95% CI for the difference between vaccine regimens calculated using the test statistic proposed by Miettinen and Nurminen (1985)[1] will be provided. In addition, the p-value by the Miettinen and Nurminen method will be provided for Tier 1 events.

Tier 1 events: These are prespecified events of clinical importance and, if any, are maintained in a list in the product's Safety Review Plan.

Tier 2 events: These are events that are not Tier 1 but are "common." An AE MedDRA preferred term (PT) is defined as a Tier 2 event if there is at least 1.0% incidence in any vaccine regimen.

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

3.5.2. Reactogenicity Data

The reactogenicity data collected in the study e-diary will include: local reactions (erythema/redness, induration/swelling, and pain at the injection site) and systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain). The e-diary will record reactogenicity data from Day 1 to Day 7 starting on the day of each vaccination.

Participants reporting local reactions and systemic events on any day within the 7-day period after each vaccination and also for any vaccination will be descriptively summarized by vaccine regimen. Severities of local reactions and systemic events reported after each vaccination and also for any vaccination will also be descriptively summarized by vaccine regimen. Exact 2-sided 95% CIs of the percentages will also be presented.

All reactogenicity endpoints will be summarized as number and percentage of participants with events by vaccine regimen. Additionally, exact 2-sided 95% CIs of the percentages will be calculated using the Clopper-Pearson method.

3.5.2.1. Local Reaction Endpoints

Local Reactions: Presence or Absence

The presence of redness or swelling is to be recorded in the e-diary as "yes" or "no." If redness or swelling is present, then a second question is to appear requesting the size of the affected area; otherwise, no question is to appear. A measuring device with a scale ranging from 1 to 21 is to be used to measure the largest diameter in whole-number increments. Measurements are to be rounded up to the nearest whole number. If the area is larger than the measuring device can measure, "21+" is to be selected. Measuring device units are converted to centimeters according to the scale: 1 measuring device unit = 0.5 centimeters (cm).

The presence of redness and swelling is defined according to the following scale:

= ., if missing

= "No," if no or minimal redness or swelling is present, <2.5 cm (<5 measuring device units)

= "Yes," if ≥2.5 cm (≥5 measuring device units)

These categories (., "no," "yes") as assessed on Day 1 to Day 7 after each vaccination will be used for derivation of the variables below.

CCI [redacted]

- Presence of each local reaction on any day (Day 1 to Day 7) after each vaccination and after any vaccination.

CCI [redacted]

- Presence of any local reaction on any day (Day 1 to Day 7) after each vaccination and after any vaccination.

For each local reaction, the derivation of CCI [redacted] "any day" is given in Table 6.

Table 6. Derived Variables for Each Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
CCI [redacted]			
Any day (Day 1 to Day 7)	Participant reported the reaction as "yes" on any day (Day 1 to Day 7)	Participant reported the reaction as "no" on all 7 days or as a combination of "no" and missing on all 7 days	Participant did not report on the reaction on any of the 7 days

For any local reaction, the derivation of CCI [redacted] "any day" is given in Table 7.

Table 7. Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
CCI [redacted]			
Any day (Day 1 to Day 7)	Participant reported any reaction as "yes" on any day (Day 1 to Day 7)	Participant reported all reactions as "no" on all 7 days or as a combination of "no" and missing on all 7 days	Participant did not report on any of the reactions on any of the 7 days

Maximum Severity for Local Reactions

Erythema/redness and induration/swelling are measured and recorded in measuring device units (range: 1-21+) and then categorized as absent, mild, moderate, or severe based on the grading scale in Table 8. Pain at the injection site will be assessed by the participants as mild, moderate, or severe according to the grading scale in Table 8.

Table 8. Local Reactions Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization for severe pain
Erythema/ Redness	2.5 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 (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Induration/ Swelling	2.5 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 (≥21 measuring device units)	Necrosis

Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. A Grade 4 reaction will be recorded in the CRF and is not collected in the e-diary. Grade 4 could also be determined if a reaction is reported as an SAE.

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

= ., if values are missing for all days (Day 1 to Day 7)

= 0, if the participant reports all reactions as "no" or a combination of missing and "no" for all days (Day 1 to Day 7)

= *highest grade* (maximum severity) within 7 days after vaccination, if the answer is "yes" for at least 1 day

Duration of Each Local Reaction

For participants experiencing any local reactions (or those with a derived reaction as described in Table 6 and Table 8), the maximum duration (last day of reaction – first day of reaction + 1) will be derived for each study vaccination. Resolution of the event is the last day on which the event is recorded in the e-diary or the date the event 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." However, if an event is ongoing at the time of a subsequent vaccination, the end date/day for the ongoing event will be the date/day that the next vaccination is administered, which will be used for the duration computation. Participants with no reported reaction have no duration.

Onset of Each Local Reaction

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

The onset day for each local reaction is the first day the participant reports the local reaction, even if the reaction later becomes more severe. The onset day for any local reaction will be the first day of any of the 3 local reactions, regardless of severity. Onset day will be "missing" for participants without the indicated local reaction.

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

1. Each local reaction on CCI any day (Day 1 to Day 7) after each vaccination and after any vaccination.
2. Any local reaction on CCI any day (Day 1 to Day 7) after each vaccination and after any vaccination.
3. Maximum severity of each local reaction on any day (Day 1 to Day 7) after each vaccination and after any vaccination.
4. Maximum duration of each local reaction after each vaccination.
5. Onset day of each local reaction after each vaccination.
6. Onset day of any local reaction after each vaccination.

3.5.2.2. Systemic Event Endpoints

Systemic events will be reported via the e-diary. Participants will be asked to assess the severity of each event as mild, moderate, or severe as specified in Table 9. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4, after physical examination or documentation from another medically qualified source.

Table 9. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Headache	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization for severe headache
Fatigue/ Tiredness	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization for severe fatigue
New or worsening muscle pain	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization for severe new or worsening muscle pain
New or worsening joint pain	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization for severe new or worsening joint pain

Abbreviation: IV = intravenous.

For each systemic event, the following variables will be derived, similar to local reactions:

1. Each systemic event on CCI [redacted] any day (Day 1 to Day 7) after each vaccination and after any vaccination.
2. Any systemic event (including fever as described in Section 3.5.2.3) on CCI [redacted] any day (Day 1 to Day 7) after each vaccination and after any vaccination.
3. Maximum severity of each systemic event on any day (Day 1 to Day 7) after each vaccination and after any vaccination.
4. Maximum duration of each systemic event after each vaccination.
5. Onset day of each systemic event after each vaccination.
6. Onset day of any systemic event after each vaccination.

The derivation of these variables is similar to the derivation of the variables for local reactions (Section 3.5.2.1).

3.5.2.3. Temperature

Oral temperature will be collected in the e-diary, in the evening, daily for 7 days after vaccination. It will also be collected at any time during the e-diary data collection periods that fever is suspected. The highest temperature for each day will be recorded in the e-diary. The protocol defines fever as an oral temperature ≥38.0°C (≥100.4°F). Fever will be categorized as specified in Table 10.

Table 10. Scale for Fever

Mild (Grade 1)	38.0-38.4°C (100.4-101.1°F)
Moderate (Grade 2)	38.5-38.9°C (101.2-102.0°F)
Severe (Grade 3)	39.0-40.0°C (102.1-104.0°F)
Potentially life threatening (Grade 4)	>40.0°C (>104.0°F)

Similar to the derivations of systemic events and local reactions, fever will be derived for the following:

1. Fever on CCI any day (Day 1 to Day 7) after each vaccination and after any vaccination.
2. Highest fever (maximum severity) on any day (Day 1 to Day 7) after each vaccination and after any vaccination.
3. Maximum duration of fever after each vaccination.
4. Onset day of fever after each vaccination.

Temperatures <35.0°C and >42.0°C will be excluded from the analysis.

3.5.3. E-Diary Completion

For any given day, an e-diary will be transmitted and considered complete if all expected data (the 3 local reactions and the 6 systemic events, including fever) are available. If all data are missing for all items on the e-diary, for all days following vaccination, the e-diary will be considered not transmitted. An e-diary will be considered completed if all expected data for all days are available (ie, not missing) and data are valid. Otherwise, the e-diary will be considered incomplete.

For e-diaries, an indicator variable for the percentage of days without data will be derived as follows:

= 1, if data have been transmitted, and are complete for 7 days (100%)

= 2, if data have been transmitted, and are complete for 6 days (≥75% to <100%)

= 3, if data have been transmitted, and are complete for 4 or 5 days (≥50% to <75%)

= 4, if data have been transmitted, and are complete for 2 or 3 days (≥25% to <50%)

= 5, if data have been transmitted, and are complete for 0 to 1 day (<25%)

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. Classifications will be documented per standard operating procedures.

4.1. Evaluable Immunogenicity Populations

The evaluable immunogenicity population assessed at Month 7 (EI7) will be the primary population for the immunogenicity analyses. The EI7 population will consist of all study participants who:

- Have been enrolled (signed the ICD) and received all 3 doses of the investigational product to which they were randomized,
- Have had blood drawn for assay testing within 28 to 47 days after Visit 4,
- Have valid and determinate assay results for either toxin A or toxin B for the specified analysis at Month 7, and
- Have no major protocol deviations.

The evaluable immunogenicity population assessed at Month 12 (EI12) will be the population for the immunogenicity analyses at Month 12. The EI12 population will consist of all study participants who:

- Have been enrolled (signed the ICD) and received all 3 doses of the investigational product to which they were randomized,
- Have had blood drawn for assay testing within 165 to 200 days after Visit 4,
- Have valid and determinate assay results for either toxin A or toxin B for the specified analysis at Month 12, and
- Have no major protocol deviations.

4.2. Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all randomized participants who have received at least 1 vaccination and have at least 1 valid and determinate assay result for either toxin A or toxin B for the proposed analysis time points. Participants will be summarized according to the vaccine group to which they were randomized.

Immunogenicity analyses using the mITT population will be conducted only if the mITT population size exceeds the size of the EI7 (or EI12 as appropriate) population by >5%. If the difference between the sizes of the mITT and EI7 (or EI12 as appropriate) populations is ≤5%, only the analyses based on the EI7 (or EI12 as appropriate) population will be provided.

4.3. Safety Analysis Population

The safety analysis population (SAF) will include all participants who have received at least 1 dose of the investigational product. For reactogenicity analyses by dose, participants who received a different investigational product regimen from the regimen they were assigned will be included in the safety population for the summaries of individual vaccinations up until the point their regimen differs from the assigned regimen, at which point they would no longer be included. For AE analysis, such participants will be included in the AE summary in the group according to the second vaccine dose received.

4.4. Other Analysis Sets

No other analysis set will be defined for the study.

5. GENERAL METHODOLOGY AND CONVENTIONS

The immunogenicity data will be summarized according to the vaccine regimen as received for participants in the EI7 (or EI12 as appropriate**)** population and according to the vaccine regimen as randomized in the mITT population.

For the assessments of seroresponse difference at Month 7, Month 12, and at Month 7 and Month 12 by age group, as well as the summary of fold rise, the *C difficile* toxin A– or toxin B–specific neutralizing antibody concentration levels below the LLOQ or denoted as BLQ will be set to the appropriate LLOQ value.

For GMC and GMFR analysis, the antibody levels that are below LLOQ or denoted as BLQ will be assigned a value of 0.5 × LLOQ. Missing serology data will not be imputed.

5.1. Hypotheses and Decision Rules

5.1.1. Analysis of the Primary Immunogenicity Endpoint

The primary objective of assessing noninferiority of the 2-dose regimen to the 3-dose regimen will be tested for each of *C difficile* toxin A– or toxin B–specific neutralizing antibody levels determined at 1 month after the last vaccination using participants in the EI7 population.

The 2 null hypotheses (H_0) for noninferiority are:

$H_{01} : \ln(\mu_2) - \ln(\mu_3) \leq -\ln(1.5)$

where $\ln(\mu_2)$ and $\ln(\mu_3)$ are the means of the natural logarithm-transformed *C difficile* toxin A– or toxin B–specific neutralizing antibody levels from participants receiving the *C difficile* vaccine 2-dose regimen and 3-dose regimen, respectively, measured 1 month after the last vaccination (Month 7) of the vaccine regimen. Baseline adjusted GMC ratios, along with 95% CIs, will be computed for each of toxin A– or toxin B–specific neutralizing antibody levels and will be used to test the null hypothesis.

and

H_{02}: $P_2 - P_3 \leq -10\%$

where P_2 and P_3 are the percentage of participants with a seroresponse in *C difficile* toxin A– or toxin B–specific neutralizing antibody levels from participants receiving the *C difficile* vaccine 2-dose regimen and 3-dose regimen, respectively, measured 1 month after the last vaccination (Month 7) of the vaccine regimen. A participant achieves seroresponse if the participant has at least a 4-fold rise in the respective antibody levels for the proposed analysis time point relative to the levels from baseline. Baseline concentration is defined as the antibody concentration results from the blood drawn before vaccine Dose 1. The difference in percentage of participants achieving seroresponse and the associated 95% CIs will be calculated using the Miettinen and Nurminen method.

The primary immunogenicity objective of the noninferiority of the 2-dose regimen to the 3-dose regimen will be achieved if the lower limit of the 2-sided 95% CI for the GMC ratio (2-dose/3-dose) is > 0.67 and the lower limit of the 2-sided 95% CI for the difference between the regimens (2-dose minus 3-dose) in the percentage of participants achieving seroresponse is > -10% for both toxin A– and toxin B–specific neutralizing antibody levels assessed 1 month after the last vaccination.

A secondary analysis will be performed based on the mITT population as appropriate. For this analysis participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

5.1.2. Analysis of the Secondary Immunogenicity Endpoint

If the primary immunogenicity objective of the noninferiority of the 2-dose regimen to the 3-dose regimen is met, the same null hypotheses (Section 5.1.1) will be evaluated for each of *C difficile* toxin A– or toxin B–specific neutralizing antibody levels at 6 months after the last vaccination (Month 12) using participants in the EI12 population.

The secondary immunogenicity objective will be evaluated by the GMC ratio first and then by the difference in percentage of participants achieving seroresponse at 6 months after the last vaccination for each *C difficile* toxin A–and toxin B–specific neutralizing antibody, based on the EI12 population and the mITT population as appropriate. Missing serology data will not be imputed.

The secondary immunogenicity objective of the noninferiority of the 2-dose regimen to the 3-dose regimen will be achieved if the lower limit of the 2-sided 95% CI for the GMC ratio (2-dose/3-dose) is > 0.67 and the lower limit of the 2-sided 95% CI for the difference between the regimens (2-dose minus 3-dose) in the percentage of participants achieving seroresponse is > -10% for both toxin A– and toxin B–specific neutralizing antibody levels assessed 6 month after the last vaccination.

5.2. General Methods

Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum. Descriptive statistics for categorical variables are n, percentage, and total (N). There is no screening period in this study, and Day 1 (Visit 1) is considered the date the participant receives his or her first vaccination.

5.2.1. Analyses for Binary Endpoints

Exact 2-sided 95% CIs will be computed using the Clopper-Pearson method.

If *r* equals the number of responses and *n* equals the number of participants, then it follows that $p = r/n$ is the estimate of the proportion of responses. An exact 95% CI (or Clopper-Pearson confidence limit) can be computed by solving the following 2 equations. For the lower limit P_L and the upper limit P_U, use:

$$P_L = \frac{rF_L}{(rF_L+(n-r+1))} \quad and \quad P_U = \frac{(r+1)F_U}{(n-r)+(r+1)F_U}$$

where F_L is the quantile from the F distribution for α=0.025, with numerator degrees of freedom equal to *2r* and denominator degrees of freedom equal to *2(n-r+1)*. F_U is the quantile from the F distribution for α=0.975, with numerator degrees of freedom equal to *2(r+1)* and denominator degrees of freedom equal to *2(n-r)*. When *r* equals 0, F_L is set to 1.0 so P_L equals 0. When *r* equals *n*, F_U is set to 1.0 so P_U equals 1. The CI using the F distribution is described in Collett (1991).[2]

For Tier 1 and Tier 2 AEs, the difference in the percentages between *C difficile* vaccine regimens will be provided. The Miettinen and Nurminen method will be used to derive the 95% CI for the risk difference between vaccine regimens. In addition, the p-value by the Miettinen and Nurminen method will be provided for Tier 1 events.

5.2.2. Analyses for Continuous Endpoints

The *C difficile* toxin A– or toxin B–specific neutralizing antibody levels at each blood sampling time point will be summarized by GMCs and the associated 95% CIs for each vaccine regimen. The GMC will be calculated as the mean of the assay levels after making the logarithm transformation and then exponentiating the result. The 2-sided 95% CI will be constructed by obtaining the CI for the mean of the logarithmically transformed assay results based on the t-distribution and then exponentiating the limits.

The adjusted GMCs and the corresponding GMC ratios will be calculated using analysis of covariance on logarithmically transformed neutralizing antibody levels at the time point with baseline antibody levels as a covariate and dose regimen as a fixed factor. The SAS GLM procedure will be used to estimate the GMC ratios and the associated 95% CIs.

5.3. Methods to Manage Missing Data

5.3.1. Safety Data

Standard algorithms for handling missing AE dates and missing AE severity will be applied following the safety rulebook summary developed by Pfizer.

Reactogenicity Data

For derived variables based on reactogenicity data, if any day of the 7-day e-diary is available, the "any day (Day 1 to Day 7)" data will be considered nonmissing. Participants are excluded from the analysis if they do not receive the particular dose or the safety data are missing for all days within the interval.

The reactogenicity data are collected through the e-diary, which does not allow participants to skip a question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all reactogenicity data for the participant on that day are nonmissing. The e-diary transmission and completion status will be summarized per Section 3.5.3. The e-diary completion summary will provide the missing data information on the reactogenicity data.

5.3.2. Immunogenicity Data

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Primary Endpoints for Immunogenicity

The primary objective for immunogenicity is to establish noninferiority of the 2-dose regimen to the 3-dose regimen for each of *C difficile* toxin A– and toxin B–specific neutralizing antibody levels by adjusted GMC ratios, adjusted for baseline antibody level, and by the difference between the regimens in the percentage of participants achieving seroresponse, evaluated at 1 month after the last vaccination (Month 7).

6.1.1.1. *C difficile* Toxin A– and Toxin B–Specific Neutralizing Antibody Levels at Visit 5

Endpoint: *C difficile* toxin A–specific neutralizing antibody levels for each regimen expressed as adjusted GMCs, adjusted for baseline antibody level.

- Analysis time point: Visit 5 (Month 7)
- Analysis population: EI7 population (and mITT population as appropriate)
- Analysis methodology: GLM procedure to calculate adjusted GMC ratio (2-dose/3-dose) and the 95% CI
- Supporting objective: primary immunogenicity objective of noninferiority.

Reporting results:

- Two-sided 95% CI for the adjusted GMC ratio (2-dose/3-dose).

Endpoint: *C difficile* toxin B–specific neutralizing antibody levels for each regimen expressed as adjusted GMCs, adjusted for baseline antibody level.

- Analysis time point: Visit 5 (Month 7).
- Analysis population: EI7 population (and mITT population as appropriate).
- Analysis methodology: GLM procedure to calculate adjusted GMC ratio (2-dose/3-dose) and the 95% CI.
- Supporting objective: primary immunogenicity objective of noninferiority.

Reporting results:

- Two-sided 95% CI for the adjusted GMC ratio (2-dose/3-dose).

Endpoint: *C difficile* toxin A–specific neutralizing antibody levels for each regimen expressed as the percentage of participants achieving seroresponse.

- Analysis time point: Visit 5 (Month 7).
- Analysis population: EI7 population (and mITT population as appropriate).
- Analysis methodology: Miettinen and Nurminen procedure to calculate percentage difference in seroresponse (2-dose minus 3-dose) and the 95% CI.
    - Supporting objective: primary immunogenicity objective of noninferiority.

Reporting results:

- Two-sided 95% CI for the percentage difference in seroresponse (2-dose minus 3-dose).

Endpoint: *C difficile* toxin B–specific neutralizing antibody levels for each regimen expressed as the percentage of participants achieving seroresponse.

- Analysis time point: Visit 5 (Month 7).
- Analysis population: EI7 population (and mITT population as appropriate).
- Analysis methodology: Miettinen and Nurminen procedure to calculate percentage difference in seroresponse (2-dose minus 3-dose) and the 95% CI.
- Supporting objective: primary immunogenicity objective of noninferiority.

Reporting results:

- Two-sided 95% CI for the percentage difference in seroresponse (2-dose minus 3-dose).

6.1.2. Primary Endpoints for Safety

The primary objective for safety is to evaluate the *C difficile* vaccine in a 2-dose and 3-dose regimen by assessing local reactions and systemic events, AEs, and SAEs.

6.1.2.1. Local Reactions and Systemic Events as Self-Reported in E-Diaries

Endpoints: (1) Local reactions (pain, erythema, and induration); (2) maximum severity as self-reported in the e-diary for up to 7 days following vaccination at Visit 1, Visit 2, and Visit 4.

- Analysis time points: occurring on CCI any day during Day 1 to Day 7 following vaccination at Visit 1, Visit 2, and Visit 4 (Months 0, 1, and 6, respectively).
- Analysis population: SAF.
- Analysis methodology: point estimates and Clopper-Pearson Cis.
- Supporting objective: primary safety objective.

Reporting results:

- The number and percentage of participants reporting: (1) a local reaction; (2) maximum severity, on CCI on any day during Day 1 to Day 7 and the associated 95% Cis.

Endpoints: (1) Systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain); (2) maximum severity as self-reported in the e-diary for up to 7 days following vaccination at Visit 1, Visit 2, and Visit 4.

- Analysis time points: occurring on CCI any day during Day 1 to Day 7 following vaccination at Visit 1, Visit 2, and Visit 4 (Months 0, 1, and 6, respectively).
- Analysis population: SAF.
- Analysis methodology: point estimates and Clopper-Pearson Cis.
- Supporting objective: primary safety objective.

Reporting results:

- The number and percentage of participants reporting: (1) a systemic event; (2) maximum severity, on CCI on any day during Day 1 to Day 7 and the associated 95% Cis.

6.1.2.2. Adverse Events

Endpoint: Nonserious AEs from the date of the first dose to Visit 5.

- Analysis time points: time of the first dose to Visit 5 (Month 7).
- Analysis population: SAF.
- Analysis methodology: point estimates and Clopper-Pearson Cis.
- Supporting objective: primary safety objective.

Reporting results:

- The number and percentage of participants reporting nonserious AEs for the duration of time of the first dose to Visit 5 and the associated 95% Cis.

Endpoint: SAEs from the date of the first dose to Visit 7.

- Analysis time points: time of the first dose to Visit 7 (Month 12).
- Analysis population: SAF.
- Analysis methodology: point estimates and Clopper-Pearson Cis.
- Supporting objective: primary safety objective.

Reporting results:

- The number and percentage of participants reporting SAEs for the duration of time of the first dose to Visit 7 and the associated 95% Cis.

6.2. Secondary Endpoints

The secondary objective for immunogenicity is to establish noninferiority of the 2-dose regimen to the 3-dose regimen for each of *C difficile* toxin A– and toxin B–specific neutralizing antibody levels by adjusted GMC ratios, adjusted for baseline antibody level, and by the difference between the regimens in the percentage of participants achieving seroresponse, evaluated at 6 months after the last vaccination (Month 12).

6.2.1. *C difficile* Toxin A– and Toxin B–Specific Neutralizing Antibody Levels at Visit 7

Endpoint: *C difficile* toxin A–specific neutralizing antibody levels for each regimen expressed as adjusted GMCs, adjusted for baseline antibody level.

- Analysis time point: Visit 7 (Month 12).
- Analysis population: EI12 population (and mITT population as appropriate).
- Analysis methodology: GLM procedure to calculate adjusted GMC ratio (2-dose/3-dose) and the 95% CI.
- Supporting objective: secondary immunogenicity objective of noninferiority.

Reporting results:

- Two-sided 95% CI for the adjusted GMC ratio (2-dose/3-dose).

Endpoint: *C difficile* toxin B–specific neutralizing antibody levels for each regimen expressed as adjusted GMCs, adjusted for baseline antibody level.

- Analysis time point: Visit 7 (Month 12).

- Analysis population: EI12 population (and mITT population as appropriate).
- Analysis methodology: GLM procedure to calculate adjusted GMC ratio (2-dose/3-dose) and the 95% CI.
- Supporting objective: secondary immunogenicity objective of noninferiority.

Reporting results:

- Two-sided 95% CI for the adjusted GMC ratio (2-dose/3-dose).

Endpoint: *C difficile* toxin A–specific neutralizing antibody levels for each regimen expressed as the percentage of participants achieving seroresponse.

- Analysis time point: Visit 7 (Month 12).
- Analysis population: EI12 population (and mITT population as appropriate).
- Analysis methodology: Miettinen and Nurminen procedure to calculate the percentage difference in seroresponse (2-dose minus 3-dose) and the 95% CI.
- Supporting objective: secondary immunogenicity objective of noninferiority.

Reporting results:

- Two-sided 95% CI for the percentage difference in seroresponse (2-dose minus 3-dose).

Endpoint: *C difficile* toxin B–specific neutralizing antibody levels for each regimen expressed as the percentage of participants achieving seroresponse.

- Analysis time point: Visit 7 (Month 12).
- Analysis population: EI12 population (and mITT population as appropriate).
- Analysis methodology: Miettinen and Nurminen procedure to calculate the percentage difference in seroresponse (2-dose minus 3-dose) and the 95% CI.
- Supporting objective: secondary immunogenicity objective of noninferiority.

Reporting results:

- Two-sided 95% CI for the percentage difference in seroresponse (2-dose minus 3-dose).

CCI

[redacted]

[redacted]

CCI

[redacted]

[redacted]

CCI

[redacted]

[redacted]

CCI

[redacted]

[redacted]

6.5. Baseline and Other Summaries and Analyses

6.5.1. Demographic and Medical History

Descriptive summary statistics of baseline demographics and medical history as described in Section 3.4 will be provided.

6.5.2. Study Conduct and Participant Disposition

The numbers and percentages of participants who signed an ICD, were randomized, were vaccinated, withdrew during the study period, and completed the study will be summarized. The reasons for withdrawal will also be tabulated. The reasons for withdrawal will be those specified in the database; no rewording/recoding will be done.

6.5.3. Concomitant Medications and Nondrug Treatments

A listing and a summary of concomitant medications and vaccinations will be provided for the duration of the study.

6.5.4. Illness Visit Outcomes, Laboratory Results

All data summaries for illness visit outcomes, laboratory results, and AEs will be provided.

6.6. Safety Summaries and Analyses

All safety analyses for AEs will be summarized in accordance with Pfizer reporting standards including all participants enrolled in the study.

6.6.1. Adverse Events

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an AE or a group of AEs. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, the purpose of safety analysis is to generate hypotheses for further investigation. The 3-tier approach facilitates this analysis.

CCI

[redacted]

8. REFERENCES

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

2. Collett D. Statistical inference for binary data. In: Modelling binary data. London, England: Chapman & Hall; 1991:17-42.

[redacted]