Protocol B5091007

A PHASE 3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF A *CLOSTRIDIUM DIFFICILE* VACCINE IN ADULTS 50 YEARS OF AGE AND OLDER

Statistical Analysis Plan (SAP)

Version: 4

Date: 02 Dec 2021

[redacted]

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LIST OF TABLES

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1. VERSION HISTORY

This statistical analysis plan (SAP), Version 4, for Study B5091007 is based on the protocol administrative change letter (PACL) dated 02 Dec 2021.

Table 1. Summary of Major Changes in SAP Amendment

SAP Version	Change	Rationale
1	Not applicable	Not applicable
2	Amendment	Amendment to reflect protocol amendment 2
3	Amendment	Amendment to reflect protocol amendments 3 and 4, and revised analysis for missing data imputation
4	Amendment	Amendment to reflect the PACL dated 02 Dec 2021, which modified the plan to stop the study and perform the final analysis due to operational futility when at least 40 first primary *Clostridium difficile* infection cases in the per-protocol-3 population have accrued.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B5091007. A brief description of the study design and the study objectives are given. Subsequent sections include analysis populations and the definitions of the efficacy and safety endpoints followed by details around statistical analysis and reporting. A list of tables, listings, and figures, mock-up tables, listings, and figures, and programming rules are prepared separately based on the methods described in this document. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

As of the PACL dated 02 Dec 2021, the study will be stopped and the final analysis will be performed due to operational futility when at least 40 first primary *Clostridium difficile* infection (CDI) cases in the per-protocol-3 (PP-3) population have accrued.

Three interim analyses were planned after 30, 40, and 50 first primary CDI cases, and only the first planned interim analysis was conducted. With this SAP amendment, while the statistical approach will remain the same, the final analysis will be conducted with all the available data at the study completion following the PACL.

2.1. Study Objectives

2.1.1. Primary Efficacy Objective

- To demonstrate that Pfizer's *Clostridium difficile* vaccine is effective in reducing the incidence of a first primary episode of CDI (case definition 1, Section 3.4.1).

[redacted]

2.1.2. Primary Safety Objective

- To evaluate the safety profile of Pfizer's *C difficile* vaccine as measured by the percentage of subjects reporting local reactions and systemic events, adverse events (AEs), and serious adverse events (SAEs).

2.1.3. Secondary Efficacy Objectives

Secondary efficacy objectives of Pfizer's *C difficile* vaccine will be evaluated for the 3-dose family and the 2-dose family after primary objectives are met. The objectives included as secondary, and the order in which they will be analyzed, were determined on the basis of their potential public health importance and their potential to be adequately powered. The objectives within each family will be evaluated sequentially in the following order:

- For the 3-dose family:

    1. To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing:

        - The incidence of all CDI cases (see case definitions 1 and 2, Section 3.4.1 and Section 3.4.2).

    2. To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing the severity of CDI, defined by:

        - The duration of CDI episodes.

        - The requirement to seek medical attention.

    3. To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing the incidence of recurrent CDI (see case definition 2, Section 3.4.2).

- For the 2-dose family (at-least-2-dose/only-2-dose family).

    - In subjects who received at least 2 doses of vaccine.

    1. To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing:

        - The incidence of all CDI cases (see case definitions 1 and 2, Section 3.4.1 and Section 3.4.2).

    2. To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing the incidence of recurrent CDI (see case definition 2, Section 3.4.2).

    - In subjects who received only 2 doses of vaccine.

    3. To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing:

[redacted]

- The incidence of a first primary episode of CDI (see case definition 1, Section 3.4.1).
- The incidence of recurrent CDI (see case definition 2, Section 3.4.2).

[redacted]

[redacted]

[redacted]

2.2. Study Design

2.2.1. Description

This is a Phase 3, placebo-controlled, randomized, observer-blinded study to evaluate the efficacy, safety, and tolerability of aluminum hydroxide (AlOH)-containing *C difficile* vaccine (200 µg total toxoid) administered as a 3-dose regimen at Months 0, 1, and 6 in adults 50 years of age and above.

[redacted]

Subjects will be randomly assigned in parallel in a 1:1 ratio to receive *C difficile* vaccine (200 µg total toxoid) or placebo (saline).

This is an event-driven study with a total target of 66 first primary CDI cases (meeting case definition 1 in the PP-3 population, Section 3.4.1 and Section 4.2) to be accrued for the study; the total enrollment number may vary depending on the incidence rate of the primary endpoint, true underlying vaccine efficacy (VE), and potential early stop for efficacy or futility.

2.2.2. Number of Subjects

It is anticipated that approximately 17,476 adults, 50 years of age and above, will be enrolled globally to accumulate 66 first primary CDI cases (meeting case definition 1, Section 3.4.1). As this is an event-driven and group-sequential (GS) study, the final enrollment number may vary depending on the incidence rate of the primary endpoint, true underlying VE, and potential to stop early for efficacy or futility. The number of subjects enrolled in each country and at each site will vary based on enrollment capabilities.

To achieve a broad representation of age groups among those 50 years of age and older, and achieve an adequate rate of CDI, the numbers of subjects intended to be enrolled in each of 4 age groups are shown in Table 2.

Table 2. Intended Number of Subjects Included in the Study, by Age Group

Category	Subcategory	Minimum Number for Inclusion	Maximum Number for Inclusion
Age	50-59 years	800 subjects	1600 subjects
	60-69 years	1600 subjects	Not limited
	70-79 years	1600 subjects	Not limited
	≥80 years	400 subjects	Not limited

On monitoring the pooled primary CDI event rates in different age groups, inclusion criteria subgroups, Charlson Comorbidity Index (CCI) subgroups, and subgroups based on other baseline factors (Table 3), once the specified minimum numbers in each age group have been achieved, if a substantially higher pooled CDI event rate is observed in some subgroups, the intention may be to stop enrollment in lower-risk subgroups and complete enrollment with the higher-risk subgroups thereafter. This is mainly to help to achieve the targeted total number of first primary cases in a timely manner.

[redacted]

Table 3. Number of Subjects in Other Categories to Be Monitored for Inclusion in the Study

Category	Subcategory
Charlson Comorbidity Index	0
	1
	2
	3
	≥4
Subject inclusion criterion 4	At least 1 inpatient hospitalization ≥2 nights' duration in the previous 12 months.
	At least 2 emergency room visits in the previous 12 months.
	At least 10 outpatient visits (primary and/or secondary care visits but excluding pharmacy and mental health visits) in the previous 12 months.
	Residence in a skilled nursing facility (a residential institution that provides professional nursing care and rehabilitation services, usually following discharge from the hospital).
	Residence in a nursing home (a residential institution that provides assistance with activities of daily living).
	Inpatient hospitalization ≥2 nights' duration scheduled ≥37 days after randomization.
	Received systemic (ie, oral or injected) antibiotics at any time in the previous 12 weeks.

Subjects withdrawn from the study after randomization will not be replaced, regardless of the reason for withdrawal.

[redacted]

2.2.3. Schedule of Activities

Table 4. Schedule of Activities

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Annual Retention Visit	Visit 7	At Time of Potential CDI Case
Visit Description	Month 0 (Vax 1)	Month 1 (Vax 2)	Month 2	Month 6 (Vax 3)	Month 7	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	165-195 Days After Visit 4	Every 280-392 Days After Visit 5[a]	Not Applicable	
Informed consent[b]	X						X[c]		
Demography[b]	X								
Clinical assessment, including medical history[b]	X								
Record nonstudy vaccinations[d]	X	X	X	X	X				
Record specified concomitant medications									X
Measure and record height and weight[b]	X								
Oral temperature[b]	X	X		X					
Urine pregnancy test (females of childbearing potential)[b]	X	X		X					
Discuss contraceptive use[d]	X	X	X	X					
Confirm eligibility[d]	X	X	X	X					
Review temporary delay criteria[b]	X	X		X					
Randomization[b]	X								
Blood draw for immunogenicity assessment[d]	X		X		X				X[c]
Vaccination	X	X		X					
Postvaccination observation (at least 30 minutes) and AE assessment	X	X		X					

[redacted]

Table 4. Schedule of Activities

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Annual Retention Visit	Visit 7	At Time of Potential CDI Case
Visit Description	Month 0 (Vax 1)	Month 1 (Vax 2)	Month 2	Month 6 (Vax 3)	Month 7	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	165-195 Days After Visit 4	Every 280-392 Days After Visit 5[a]	Not Applicable	
Review stool sample collection and shipping instructions with the subject and ensure understanding	X	X	X	X	X	X	X		
Issue or send a stool collection kit and shipping box, and provide instructions on their use, as required	X	X	X	X	X	X	X		
Issue measuring device and thermometer and provide instructions on their use, as required	X	X		X					
Review subject communication methods (including for e-diary completion), assist the subject with downloading the app, or issue provisioned device, if required	X	X	X	X	X	X	X		
Record AEs	X	X	X	X	X[f]				X[f]
Record SAEs	X	X	X	X	X	X			
Capture major protocol violations		X	X	X	X	X	X	X	X
Telephone contact visit						X[g]		X	X
Electronic reminders		←	—	—	—	—	—	→	
Telephone contact for subjects unresponsive to electronic reminders		←	—	—	—	—	—	→	
Provision of stool sample									X
Completion of diarrheal episode questionnaire									X

[redacted]

Table 4. Schedule of Activities

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Annual Retention Visit	Visit 7	At Time of Potential CDI Case
Visit Description	Month 0 (Vax 1)	Month 1 (Vax 2)	Month 2	Month 6 (Vax 3)	Month 7	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	165-195 Days After Visit 4	Every 280-392 Days After Visit 5[a]	Not Applicable	
Subject completes e-diary	X	X		X					
Review e-diary data		←				→			

Abbreviations: CDI = *Clostridium difficile* infection; e-diary = electronic diary; Vax = vaccination; → = ongoing/continuous event.

a. Following approval of protocol amendment 3, subjects already enrolled in the study should have an annual retention visit arranged at the earliest opportunity, and then every 280 to 392 days thereafter.
b. Prior to vaccination.
c. At the first annual retention visit only or potential CDI visit, whichever occurs first.
d. Prior to vaccination, if at a vaccination visit.
e. Optimally within 48 hours of the third unformed stool (Bristol stool chart types 5-7).
f. Any AEs occurring up to 48 hours after each blood draw must be recorded.
g. Visit is intended to be conducted by telephone but, if desired, may be conducted in person.

[redacted]

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

3.1.1. Primary Efficacy Endpoints

- First primary CDI incidence, as defined by case definition 1 (Section 3.4.1), per 1000 person-years of follow-up, assessed during up to 2 time periods (each analysis will be performed only if the preceding one was successful).
    - After receipt of the third dose of investigational product onwards.
    - After receipt of the second dose of investigational product onwards.

3.1.2. Primary Safety Endpoints

- Local reactions (pain, erythema, induration), as self-reported on electronic diaries (e-diaries) for up to 7 days following each dose of investigational product.
- Systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, new or worsening joint pain), as self-reported on e-diaries for up to 7 days following each dose of investigational product.
- Nonserious AEs from signing of the informed consent document (ICD) to 1 month after receipt of the third dose of investigational product.
- SAEs from signing of the ICD to 6 months after receipt of the third dose of investigational product.

3.2. Secondary Endpoints

3.2.1. Secondary Efficacy Endpoints

The following endpoints are numbered to denote the order of evaluation.

- For the 3-dose family:
    1. The CDI incidence per 1000 person-years of follow-up, assessed after receipt of the third dose of investigational product onwards, of all CDI cases according to case definitions 1 and 2 (Section 3.4.1 and Section 3.4.2).
    2. (a) Mean time to resolution of diarrhea in first primary episodes of CDI (case definition 1, Section 3.4.1).

       (b) Proportion of subjects experiencing a first primary episode of CDI (case definition 1, Section 3.4.1) who have a non–protocol-related medically attended visit during the CDI episode.

3. CDI incidence per 1000 person-years of follow-up, assessed after receipt of the third dose of investigational product onwards, of recurrent CDI cases (see case definition 2, Section 3.4.2).

For the 3-dose family, each analysis will be performed only if the preceding analysis resulted in a statistically significant vaccine effect.

For the 2-dose family: subjects who received at least 2 doses of vaccine:

1. CDI incidence per 1000 person-years of follow-up, assessed after receipt of the second dose of investigational product onwards of all CDI cases according to case definitions 1 and 2 (Section 3.4.1 and Section 3.4.2).

2. CDI incidence per 1000 person-years of follow-up, assessed after receipt of the second dose of investigational product onwards of recurrent CDI cases according to case definition 2 (Section 3.4.2).

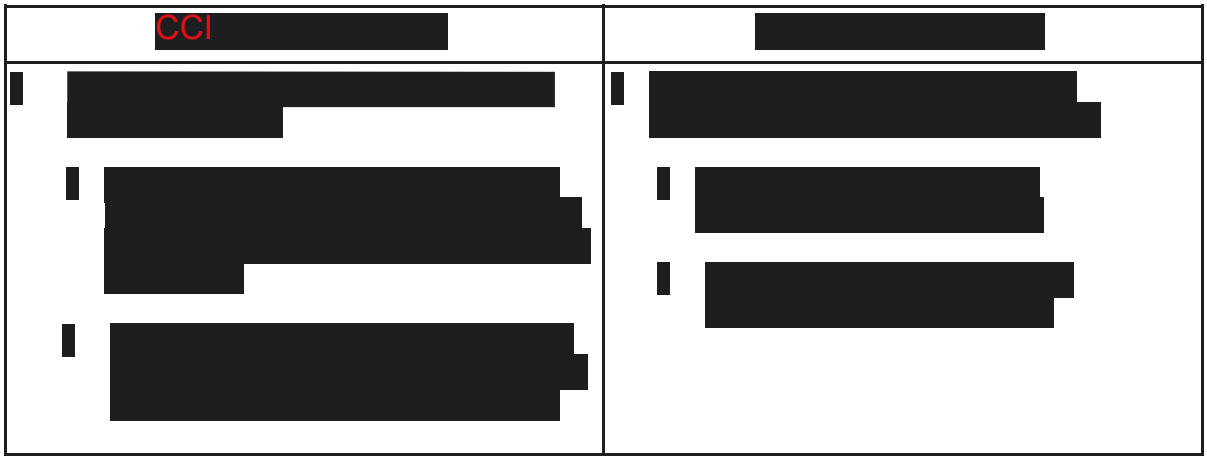
For the 2-dose family: subjects who received only 2 doses of vaccine:

3. (a) The incidence of a first primary episode of CDI (see case definition 1, Section 3.4.1), assessed after receipt of the second dose but before the third dose of investigational product.

   (b) The incidence of recurrent CDI (case definition 2, Section 3.4.2), assessed after receipt of the second dose but before the third dose of investigational product.

For the 2-dose family, each analysis will be performed only if the preceding analysis resulted in a statistically significant vaccine effect.

CCI [redacted]



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3.4. CDI Case Definitions

For all definitions, an episode will be considered to have resolved once there have been at least 2 days without passage of 3 or more unformed stools (Bristol stool chart types 5-7) and there is no further need for antibiotic treatment for CDI.

For the purposes of analyses based upon case definitions 1 and 2 (described below), all collected stool samples will be tested at the central laboratory; however, only results from valid samples (ie, samples were from subjects who fulfill the clinical aspects of the case definition, and samples were successfully transported and stored within the required time period) will be included in the main analyses.

3.4.1. Definition 1 – Primary Episode

A primary episode of CDI (ie, no previous CDI onset in the prior 8 weeks) is defined as either:

- Presence of diarrhea, defined as passage of 3 or more unformed stools (Bristol stool chart types 5-7) in 24 or fewer consecutive hours; and
- Stool sample that is positive for the toxin B gene (via PCR) and positive for toxin A and/or toxin B, as measured in the central laboratory.

or:

- Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that is positive for toxin B gene (via PCR) as measured in the central laboratory.

3.4.2. Definition 2 – Recurrent Episode

An episode of CDI that occurs 8 weeks or less after the onset of a previous CDI episode (provided the symptoms of the previous episode had resolved), defined as either:

- Presence of diarrhea, defined as passage of 3 or more unformed stools (Bristol stool chart types 5-7) in 24 or fewer consecutive hours; and
- Stool sample that is positive for the toxin B gene (via PCR) and positive for toxin A and/or toxin B, as measured in the central laboratory.

or:

- Pseudomembranous colitis diagnosed at colonoscopy, at surgery, or histopathologically; and corresponding stool sample that is positive for toxin B gene (via PCR) as measured in the central laboratory.

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3.5. Other Endpoints

3.5.1. All-Cause Death, Diarrhea

Deaths will be recorded for the entire study duration. Death is defined as any subject who died during the active study. All-cause death includes deaths for any reason.

Diarrhea will be captured in the case report form (CRF) from the time of signing the ICD to the date the subject completes or withdraws from the study.

3.6. Baseline Variables

Day 1 is defined as the day of vaccination (Visit 1, Month 0) and also the start of when local reactions and systemic events are to be reported in the e-diary.

3.7. Safety Endpoints

3.7.1. Adverse Events

The time period for actively eliciting and collecting AEs and SAEs for each subject begins from the time the subjects provides informed consent, through and including the 1-month follow-up visit (Visit 5) after Vaccination 3. The collection of SAEs continues throughout the follow-up phase through 6 months after Vaccination 3. Additionally, any AEs occurring up to 48 hours after each blood draw (Visit 5) and at the time of a potential CDI case will be reported.

All events are collected on the CRF and will be categorized according to the current version (at the time of reporting) of the Medical Dictionary for Regulatory Activities (MedDRA).

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 5.2.1.2).

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." A MedDRA preferred term is defined as a tier 2 event if its incidence is ≥1.0% in any vaccine group.

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

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

3.7.2. 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, following investigational product administration.

[redacted]

3.7.2.1. Local Reactions 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 1 measuring device unit = 0.5 centimeters.

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 redness or swelling is ≥2.5 cm (≥5 measuring device units)

These categories (., No, Yes) will be used for derivation of the variables below. For the data summary of the presence (Yes or No) of a local reaction, the following variables are required:

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

The derivation of [redacted] "any day" variables is given in Table 5.

[redacted]

Table 5. Derived Variables for Each Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
CCI [redacted]	[redacted]	[redacted]	[redacted]
Any day (Days 1-7)	Subject reports the reaction as "Yes" on any day (Day 1-7).	Subject reports the reaction as "No" on all 7 days or as a combination of "No" and missing on all 7 days.	Subject does not report on the reaction on all 7 days.

For any local reaction on any day, a similar rule applies as specified in Table 6.

Table 6. Derived Variables for Any Local Reaction

Variable	Yes (1)	No (0)	Missing (.)
CCI [redacted]	[redacted]	[redacted]	[redacted]
Any day (Days 1-7)	Subject reports any reaction as "Yes" on any day (Days 1-7).	Subject reports all reactions as "No" on all 7 days or as a combination of "No" and missing on all 7 days.	Subject does not report on any of the reactions (or reports a combination of "No" and missing) 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 7. Pain at the injection site will be assessed by the subjects as mild, moderate, or severe according to the grading scale in Table 7.

Table 7. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Interferes with activity	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

[redacted]

Only an investigator or medically qualified person is able to classify a subject's local reaction as Grade 4. 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 (Days 1-7);

= 0, if the subject reports all reactions as "No" or a combination of missing and "No" for all days (Days 1-7);

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

Duration of Each Local Reaction

For subjects experiencing any local reactions (or those with a derived reaction as described in Table 7), 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 subject diary-recording period (end date collected on the CRF). 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 would be the date/day that the next vaccine is administered, which will be used for the duration computation. Subjects 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 subject 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 subjects without the indicated local reaction.

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

1. Each local reaction on CCI [redacted] any day (Days 1-7) after each vaccination and after any vaccination.

2. Any local reaction on CCI [redacted] any day (Days 1-7) after each vaccination and after any vaccination.

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

4. Maximum duration of each local reaction after each vaccination.

[redacted]

5. Onset day of each local reaction after each vaccination.

6. Onset day of any local reaction after each vaccination.

3.7.2.2. Systemic Events Endpoints

Systemic events will be reported via the e-diary. Subjects will be asked to assess the severity of each event as mild, moderate, or severe according to Table 8. Only an investigator is able to classify a subject's systemic event as Grade 4, after physical examination or documentation from another medically qualified source.

Table 8. 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 available, similar to local reactions:

1. Each systemic event on CCI [redacted] any day (Days 1-7) after each vaccination and after any vaccination.

2. Any systemic event (including fever as described in Section 3.7.2.3) on CCI [redacted] any day (Days 1-7) after each vaccination and after any vaccination.

3. Maximum severity of each systemic event on "any day (Days 1-7)" 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.

[redacted]

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 3.7.2.1).

3.7.2.3. Temperature

Oral temperature will be collected in the e-diary, in the evening, daily for 7 days after vaccination. 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 shown in Table 9.

Table 9. 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:

1. Fever on each day and any day (Days 1-7) after each vaccination and after any vaccination.

2. Highest fever (maximum severity) on any day (Days 1-7) 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.

3.8. Study Conduct

3.8.1. E-Diary Completion

For any given day, an e-diary will be transmitted and considered to be 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 any given day, an e-diary will be considered complete if all expected data are available.

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

[redacted]

= 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%)

3.8.2. Demographic, Medical History, and Baseline Characteristics

Demographic variables collected include sex, race, ethnicity, and date of birth. The categories collected for race include:

- Black or African American
- American Indian or Alaskan native
- Asian
- Native Hawaiian or other Pacific Islander
- White
- Other

Ethnicity categories collected include:

- Hispanic or Latino
- Not Hispanic/not Latino

For countries where full date of birth is collected, age at the time of vaccination (in years) will be derived as:

> Age at vaccination = (vaccination date – date of birth + 1) / 365.25, and rounding down.

For countries where full date of birth is not collected:

- If only month and year can be collected, 01 will be entered for the day in the CRF data.

- If only year is permitted, 01 for the day and JUL (for July) for the month will be entered in the CRF data.

Medical history will be categorized according to the current version (at the time of reporting) of MedDRA.

Physical examination may be assessed prior to vaccination and will be recorded in the CRF as yes or no to the presence of any clinically significant findings. Details related to clinically significant findings will also be recorded as medical history in the CRF.

[redacted]

3.8.3. Nonstudy Vaccines and Concomitant Medications

The following concomitant medications and vaccinations will be recorded on the CRF:

- All vaccinations received from 28 days prior to study enrollment until Visit 5 (Month 7, 1 month after the third vaccination).
- At the time of a suspected CDI case, the start date, name of medication, dose, unit, route, and frequency will be recorded for the following:
  - Antibiotic use within the 12 weeks prior to the onset of the suspected CDI case.
  - Antibiotic use for the treatment of the suspected CDI case.
  - Known immunosuppressant medication, or radiotherapy use, within the 6 months prior to the onset of the suspected CDI case.
  - Systemic corticosteroid use within the 28 days prior to the onset of the suspected CDI case.
  - Proton-pump inhibitor use within the 12 weeks prior to the onset of the suspected CDI case.

Nonstudy vaccines and concomitant medications will be categorized according to the current version (at the time of reporting) of the World Health Organization (WHO) Drug Dictionary.

4. ANALYSIS SETS

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

4.1. Modified Intent-to-Treat Analysis Set

Three (3) modified intent-to-treat (mITT) populations, mITT-1, mITT-2, and mITT-3, will be defined and will be supportive populations used to analyze VE endpoints from immediately after or from 14 days after receipt of each dose of investigational product.

- mITT-1: includes all randomized subjects who received Dose 1 of investigational product.
- mITT-2: includes all randomized subjects who received Dose 1 and Dose 2 of investigational product. This population is a subset of the mITT-1 population.
- mITT-3: includes all randomized subjects who received Dose 1, Dose 2, and Dose 3 of investigational product. This population is a subset of the mITT-2 population.

Efficacy data will be summarized utilizing these populations, and subjects will be reported by randomized vaccine group, regardless of investigational product received.

4.2. Per-Protocol Analysis Set

Two (2) subject-level per-protocol (PP) populations, PP-2, PP-3, will be defined and will be the primary populations for efficacy endpoint reporting. Efficacy endpoints associated with subjects in the PP populations will only include cases and surveillance times occurring from 14 days after receipt of Dose 2, and Dose 3, for populations PP-2, and PP-3, respectively.

- PP-2: includes all randomized subjects who received Dose 1 and Dose 2 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after Dose 2. This population is a subset of the mITT-2 population.

- PP-3: includes all randomized subjects who received Dose 1, Dose 2, and Dose 3 of the investigational product to which they were randomized and had no major protocol violations up to and including 14 days after Dose 3. This population is a subset of the PP-2 population and it is also a subset of the mITT-3 population.

A major protocol violation is a protocol violation that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of efficacy (eg, subject receipt of a prohibited medication that might affect efficacy outcome, a medication error with suspected decrease in potency of the vaccine, etc. CCI [redacted] CCI [redacted]

The global medical monitor from the sponsor will identify the major protocol violations before the unblinding and locking of the efficacy analysis database.

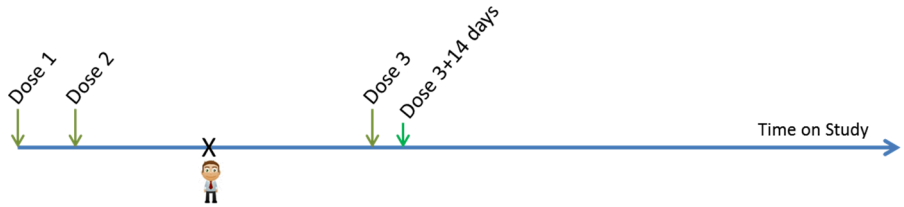
Once a major protocol violation has been identified for a subject, that subject will be viewed as having that major protocol violation from that time until the end of the subject's participation in the study (ie, a subject cannot be considered PP for various periods of time after an applicable dose).

If a subject has accumulated any time starting 14 days after a dose and prior to experiencing a first major protocol violation, the subject will remain in any applicable PP populations. In other words, if a subject qualifies for PP-X membership 14 days after Dose X, the subject will remain a member of population PP-X even if he or she experiences a major protocol violation later in the study. For example, if a subject received Dose 1, Dose 2, and Dose 3 of the investigational product and had the first major protocol violation 14 days after Dose 3, the subject cannot be a member of the PP-3 population. However, if a subject had the first major protocol violation 15 days after Dose 3, he or she would have accumulated a day, fulfilling the requirements for membership in the PP-3 population, and would remain in the PP-3 population throughout the duration of the study.

The effect of the first major protocol violation will be managed by assessing the protocol violation's impact on the surveillance times associated with the various endpoints and will be explained in Section 4.3. The following diagrams depict various scenarios related to the PP-3 and mITT-3 populations.

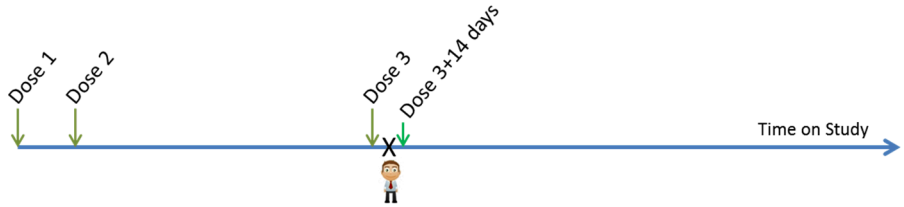
[redacted]

Scenario 1



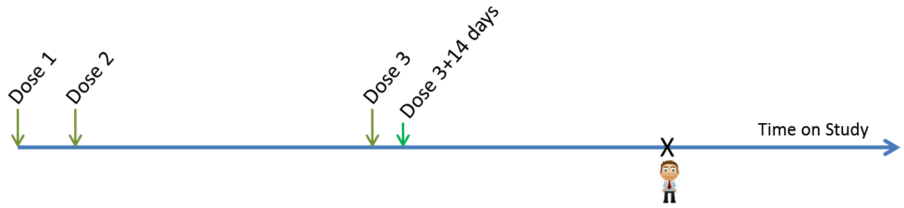
Subject is not yet in the PP-3 population. (Note: Subject is also not yet in the mITT-3 population.)

Scenario 2



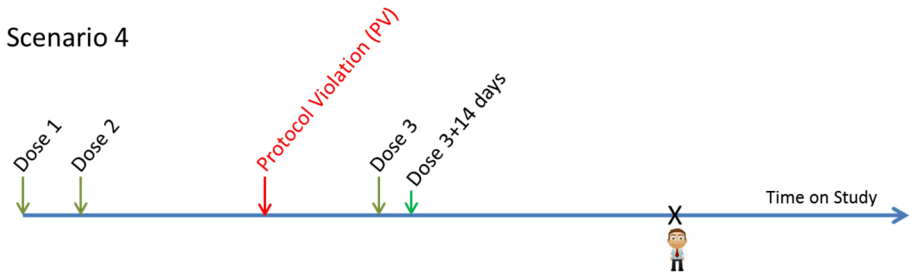
Subject is not yet in the PP-3 population. (Note: Subject is in the mITT-3 population.)

Scenario 3



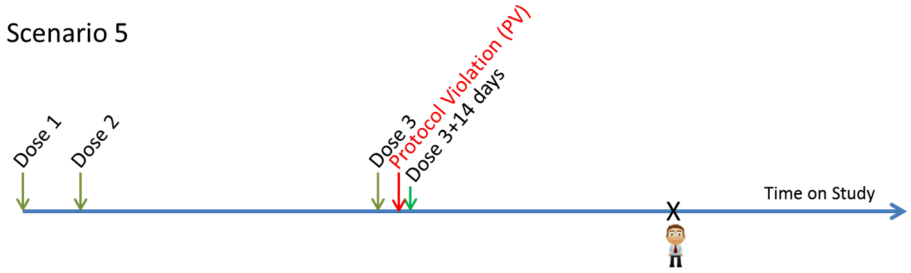
Subject is in the PP-3 population. (Note: Subject is also in the mITT-3 population.)

[redacted]



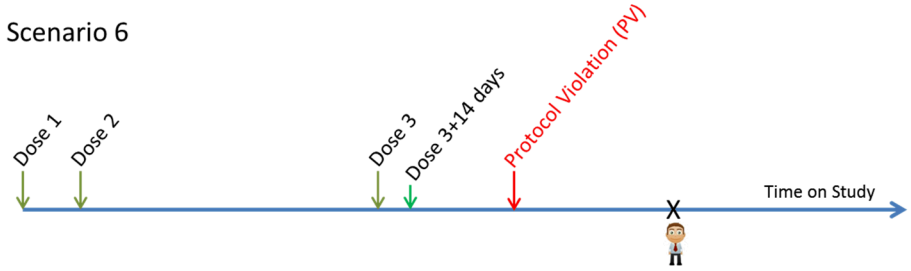
Subject is NOT in the PP-3 population because of a major protocol violation that occurred on or prior to Dose 3 + 14 days.

(Note: Subject is in the mITT-3 population since this population is not affected by a major protocol violation.)



Subject is NOT in the PP-3 population because of a major protocol violation that occurred on or prior to Dose 3 + 14 days.

(Note: Subject is in the mITT-3 population.)



Subject is in the PP-3 population even though a major protocol violation occurred because it occurred after 14 days after Dose 3. (Note: Subject is also in the mITT-3 population.)

Membership in the PP-2 population is similar to that in the PP-3 population. Membership in the mITT-3, mITT-2, and mITT-1 populations is similar to that in the PP-3 and PP-2 populations except for elimination of the +14-day window after the dose dates and elimination of the influence of the major protocol violation.

[redacted]

For inclusion in the PP-3 population, the +14-day window will be computed as follows:

If Dose 3 occurs on 01 Jan 2017, +14 days after Dose 3 will be 15 Jan 2017. If a major protocol violation occurs on 15 Jan 2017, then the subject cannot be a member of the PP-3 population. If a major protocol violation occurs on 16 Jan 2017, the subject can be a member of the PP-3 population, assuming the subject fulfills all other requirements for the population, and the subject will remain in the population through the entire duration of the study.

For inclusion in the mITT-3 population, assuming a subject received Dose 1 and Dose 2, and Dose 3 occurs on 01 Jan 2017, then the subject will be a member of the mITT-3 population starting on 01 Jan 2017 and through the remainder of the study.

Similar logic applies to the mITT-1, mITT-2, and PP-2 populations.

4.3. Identification of Endpoint Surveillance Times and Cases

Fundamental to this VE trial is the surveillance for cases satisfying various endpoints within each subject that may occur during the trial. Endpoint and subject combinations where surveillance is applicable require identification of the start and the end of the surveillance period in order to determine the subject-level endpoint surveillance time. For all VE-related endpoints in this study, the start-of-surveillance times are summarized as follows:

Endpoint's Associated Subject-Level Population	Start-of-Surveillance Time
PP-3	Dose 3 + 14 days
mITT-3[a]	Dose 3
PP-2	Dose 2 + 14 days
mITT-2[a]	Dose 2
mITT-1	Dose 1

a. Additional analyses by mITT-3/mITT-2 will be performed for the primary objective with surveillance time starting from Dose 3 + 14 days and from Dose 2 + 14 days for the mITT-3 and mITT-2 populations, respectively.

For all VE-related endpoints in this study, the end of a surveillance period is the earliest of the following events:

- When the first case of interest satisfying the endpoint occurs for endpoints that involve identification of only 1 case.
- When the end of the study occurs.
- When the subject withdraws from the study (eg, death).
- When the subject has his/her first major protocol violation after the start of the surveillance period for PP-related endpoints.
- For endpoints restricted to after Dose 2 but before Dose 3, the day of the third dose or the day the third dose was expected (168 days after Dose 2).

[redacted]

Specific information regarding VE-related endpoint surveillance start and end times by endpoint will be provided in Analysis and Reporting Plan specification documents.

Consider the primary efficacy endpoint described in the protocol as follows:

- First primary CDI incidence as defined by case definition 1 per 1000 person-years of follow-up, assessed during up to 2 time periods (each analysis will be performed only if the preceding one was successful).
    - After receipt of the third dose of investigational product onwards.
    - After receipt of the second dose of investigational product onwards.

Since these endpoints will be assessed for both the mITT and the PP populations after Dose 3 and Dose 2, they can be further broken down as follows:

1. First primary definition 1 case, which must occur on or after Dose 3 + 14 days in subjects in the PP-3 population, but before a major protocol violation.
2. First primary definition 1 case, which must occur after Dose 3, but could be the same day as Dose 3, in subjects in the mITT-3 population.
3. First primary definition 1 case, which must occur on or after Dose 2 + 14 days in subjects in the PP-2 population, but before a major protocol violation.
4. First primary definition 1 case, which must occur after Dose 2, but could be the same day as Dose 2, in subjects in the mITT-2 population.
5. First primary definition 1 case, which must occur on or after Dose 3 + 14 days in subjects in the mITT-3 population.
6. First primary definition 1 case, which must occur on or after Dose 2 + 14 days in subjects in the mITT-2 population.

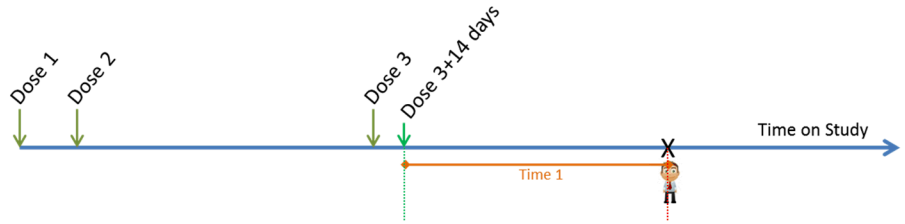
These endpoints involve surveillance for a case satisfying the defined endpoint. That surveillance time for an endpoint may include a case that satisfies the endpoint definition, or it may not. The surveillance time, even when no associated case has been identified, is meaningful and will be used in assessing VE because it represents "at-risk" time.

Consider the following endpoint:

1. First primary definition 1 case, which must occur on or after Dose 3 + 14 days in subjects in the PP-3 population, but before a major protocol violation.

The way surveillance time and the possible case are identified for this endpoint is illustrated in the following figures (Note: For these scenarios, assume "Event 1" fulfills the requirements to be a subject's first primary definition 1 case):

Scenario 3.1

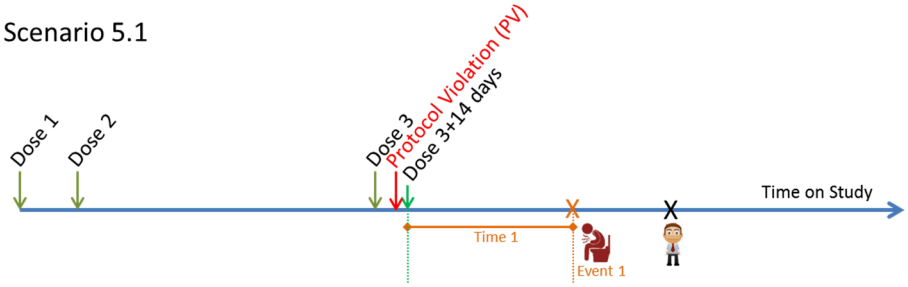


The subject has not had any event yet, but may in the future.

The subject is a member of the PP-3 population and may experience events that could be considered PP-3–related cases.

Time 1 is used for the subject's surveillance time for this endpoint even if the subject does not experience an event that could be considered a case for this endpoint.

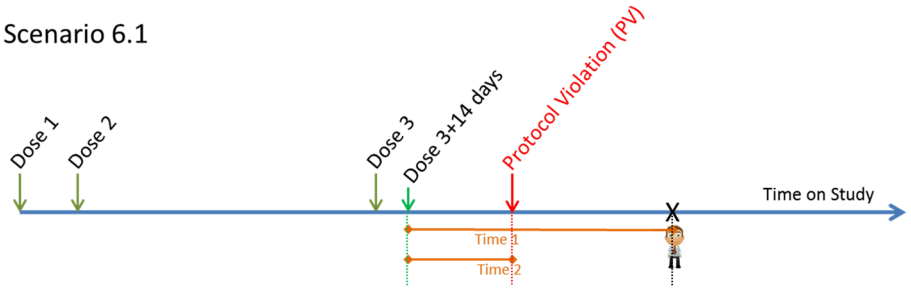
Scenario 5.1



There would be no surveillance time for the endpoint since the subject is not in the PP-3 population because of the major protocol violation that occurred on or prior to Dose 3 + 14 days.

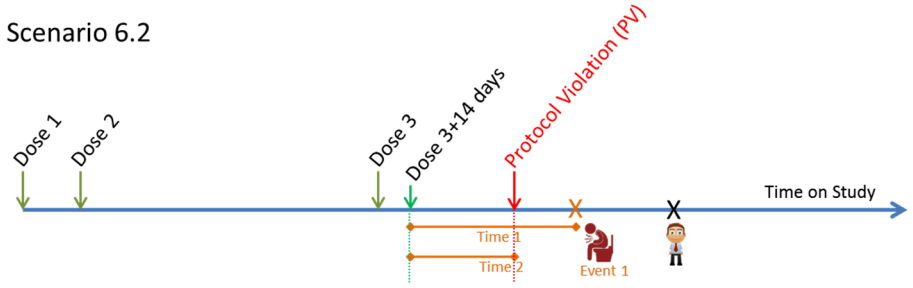
Time 1 would not be used even if Event 1 were the subject's first primary definition 1 case.

Scenario 6.1



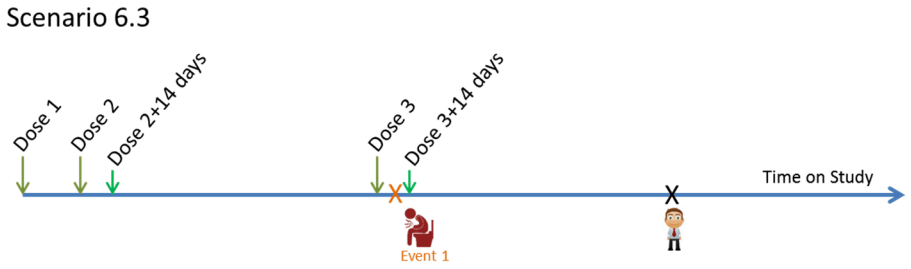
The surveillance time for this endpoint is Time 2, which is from Dose 3 + 14 days to the major protocol violation. There is a surveillance time for this endpoint even though there happened to be no event.

[redacted]



The surveillance time for this endpoint is Time 2, which is from Dose 3 + 14 days to the major protocol violation.

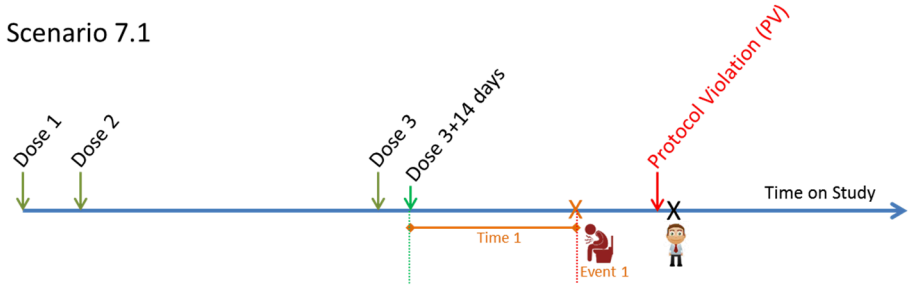
Time 1 would not be used because Event 1 occurred after the major protocol violation. The major protocol violation ended the surveillance times for all PP-3–related cases. Furthermore, Event 1 could not be counted as a case for this endpoint because it occurred after the PP-3 surveillance time.



The subject is a member of the PP-3 population.

There is no surveillance time for this endpoint because this subject's first primary definition 1 case occurred prior to Dose 3 + 14 days.

Event 1 cannot be counted for this endpoint. (It could be counted for the similar PP-2 endpoint since it occurred after Dose 2 + 14 days.)



Event 1 does count as the subject's first primary definition 1 case towards the PP-3–related endpoint because it occurred within the applicable surveillance time for such a case between Dose 3 + 14 days and the major protocol violation.

Time 1 is the surveillance time associated with this case because the surveillance time ends at the start of the case.

[redacted]

Some subjects will have multiple events and these events may occur at times other than on or after Dose 3 + 14 days. Many of the secondary CCI endpoints are designed to identify these events as cases suitable for VE analysis. Further details regarding the logic used for each endpoint will be provided in the Analysis and Reporting Plan specification documents.

4.4. Safety Analysis Set

All subjects who received at least 1 dose of investigational product (*C difficile* vaccine or placebo) will be included in the safety population. For reactogenicity analyses by dose, subjects who received a different vaccine from the vaccine they were assigned will be included in the safety population for the summaries of individual vaccinations up until the point their vaccine differs from the assigned one, at which point they will no longer be included. For AE analyses, such subjects will be included in the AE summary tabulations in the group according to the first vaccine dose received. The safety analysis set is the primary population for the safety endpoints.

4.5. Other Analysis Sets

No other analysis sets will be defined in this study.

4.6. Vaccine Misallocations

- Vaccinated but not randomized: these subjects will be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received, but will be excluded from efficacy analyses.

- Randomized but received incorrect vaccine: these subjects will be included in the mITT population for efficacy analyses if data are available and will be reported under the vaccine group based on the randomized vaccine. These subjects will also be included in the safety population for safety analysis and will be reported under the vaccine group based on the vaccine received for the analyses by dose. For the safety analysis based on the entire study period, subjects will be included in the safety population according to the first vaccine received.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Final Analysis

The primary efficacy hypotheses will be tested for null hypothesis VE ≤20% by a fixed-sequence testing procedure, with a testing order of H_{03} followed by H_{02} using only the first primary CDI cases occurring from 14 days after receipt of the third dose of investigational product, followed by those occurring from 14 days after receipt of the second dose of investigational product. The included cases will be from subjects in the primary PP populations (primary analysis populations for the primary efficacy endpoints in Table 16).

[redacted]

The hierarchical order is:

1. H_{03}: $VE_3 \leq 20\%$ vs H_{a3}: $VE_3 > 20\%$

2. H_{02}: $VE_2 \leq 20\%$ vs H_{a2}: $VE_2 > 20\%$

Where H_{0i} and H_{ai} represent the null hypothesis and alternative hypothesis and VE_i (i = 2, 3) represents VE after at least 2 doses and after all 3 doses, respectively.

VE and corresponding exact confidence intervals (CIs) are derived as described in Section 5.2.2.2. The type I error is adjusted to $\alpha = 0.018$ (1-sided) for the final analysis to account for multiplicity. At the final analysis, the null hypothesis H_{03} will not be rejected if the lower bound of the 96.4% exact CI for VE_3 is ≤20% and testing will end. If the lower bound of a 2-sided 96.4% exact CI for VE_3 (adjusted for multiplicity) is greater than 20%, then the decision will be to reject H_{03} and the analysis for H_{02} will be performed with the same level of type I error. For the H_{02} analysis, if the lower bound of the 96.4% exact CI for VE_2 is >20%, H_{02} will be rejected.

5.1.2. Interim Analyses

Prior to the PACL dated 02 Dec 2021, three (3) planned formal interim analyses were to be performed by the independent statistical team (IST) to assess whether there is overwhelming efficacy or futility with respect to the end-of-study success criterion. The following section describes the plan for these interim analyses that was in place prior to the PACL.

The first, second, and third interim analyses are planned after 30, 40, and 50 first primary CDI cases, respectively, have occurred from 14 days after receipt of the third dose of investigational product for subjects in the PP-3 population. The data cutoff date will be the calendar date of the confirmed 30th, 40th, or 50th case of first primary CDI occurring 14 days after the third dose by the central laboratory. Only the first primary efficacy endpoint will be examined. The statistical hypotheses testing (H_{03}) will be performed on interim data; H_{02} will be tested if H_{03} is rejected and a decision is made to proceed to the final analysis.

The interim-analysis alpha level is adjusted to $\alpha = 0.006$ (1-sided) for both the first and second interim analyses (IA1 and IA2), and $\alpha = 0.009$ (1-sided) for the third interim analysis (IA3), to account for multiple comparisons on the primary efficacy endpoint. For each of the first and second interim analyses, if the lower bound of the 98.8% exact CI >20%, H_{03} will be rejected and the *C difficile* vaccine will be considered efficacious; for the third interim analysis, if the lower bound of the 98.2% exact CI >20%, H_{03} will be rejected and the *C difficile* vaccine will be considered efficacious. If H_{03} is rejected, the trial will be considered successful at the interim analysis and may be stopped because of the demonstrated VE. If the decision is made to stop the trial based on demonstration of VE_3 at the interim analysis, the testing of the additional sequential hypothesis test (H_{02}) and the analyses for the secondary VE endpoints will proceed at the 0.018 (1-sided) significance level, as these analyses will be considered as final analyses. If the hypothesis test H_{03} fails to be rejected, the hypothesis test H_{02} will not be performed at the interim analysis.

[redacted]

Study futility at each interim analysis will be evaluated based on the preidentified case split (*C difficile* vaccine vs placebo) by analysis of conditional power (CP). The conditional probability of study success at the final analysis with observed VE of at least 59.6% (19 out of 66 cases) is calculated based on assumed case split in the *C difficile* vaccine group and the adjusted true VE of 66.5% remains for the rest of the study. The case split for futility is 11 vs 19 for IA1 (corresponding to a CP cutoff of 50%), 13 vs 27 for IA2 (corresponding to a CP cutoff of 60% at 40 cases), and 16 vs 34 for IA3 (corresponding to a CP cutoff of 60% at 50 cases). These futility boundaries may be subject to change to reflect subsequent program-related decisions by the sponsor.

Incorporation of the planned interim analyses is a source of multiplicity and its effect on the overall type I error for the study is accounted for in the CI adjustments for H_{03} at the interim analyses and at the final analysis. These values were chosen to be consistent with the statistical design operating characteristics put forth in the protocol, which utilized a GS design with 3 interim analyses at 30, 40, and 50 first primary CDI cases, respectively, and a gamma (-2) alpha spending function. The protocol provides an example of the statistical design operating characteristics under particular anticipated counts of total cases at the interim analyses and final analysis.

As of the PACL dated 02 Dec 2021, the first interim analysis with 30 cases of first primary CDI was conducted as planned in protocol amendment 4. The recommendation from the external data monitoring committee (E-DMC) was to continue the study because the criteria to stop for efficacy or futility were not met. Due to operational futility of slow case accrual and increased subject withdrawals, the study will be stopped and a final analysis will be performed with all available data at the completion of the study following the PACL.

For the final analysis of the first primary endpoint, the VE CI with an alpha level of 0.018 (1-sided), which was planned for the final analysis, will be used in the VE evaluation (Section 5.1.1). Since only 1 interim analysis (with 1-sided alpha level of 0.006) was conducted, the overall type I error for this primary efficacy endpoint is still controlled at the 0.025 level.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

Unblinding and reporting of the primary endpoint and all other secondary CCI [redacted] endpoints will occur after all data are cleaned and certified for analysis per relevant Pfizer standard operating procedures.

5.1.4. Adjusting for Multiplicity

5.1.4.1. Primary Endpoints

There are 2 primary efficacy hypotheses: H_{03} and H_{02}. H_{03} is followed by H_{02} if H_{03} is rejected. The study will be considered successful if H_{03} is rejected.

There are 2 sources of multiplicity in the study. First, there are repeated analyses of the primary hypothesis, H_{03}, at the interim and final analyses. Type I error adjustment due to the planned interim analysis is explained in Section 5.1.2.

The second source of multiplicity is due to the multiple primary hypotheses. The same type I errors (0.006 [1-sided] for IA1 and IA2, 0.009 [1-sided] for IA3, and 0.018 [1-sided] for final analysis) will be used for the 3-dose hypothesis (H_{03}) testing. The 2-dose hypothesis testing will be performed only if the 3-dose hypothesis is rejected. It is expected that additional first primary CDI cases occurring in the interval between Doses 2 and 3 will result in greater than 90% power to conclude true VE >20% after 2 or more doses of vaccine, assuming that the vaccine first successfully demonstrates VE >20% following 3 doses of vaccine.

Study futility will be assessed at each interim analysis. There will be no multiplicity adjustment for the futility evaluations.

5.1.4.2. Secondary Endpoints

In order to control overall type I error, and specifically the type I error for the evaluation of the secondary objectives, an alpha level of 0.018 (1-sided) for the final analysis is split equally (the Bonferroni correction, alpha = 0.009 [1-sided], for each family evaluation) for the evaluation of the secondary objectives between the 3-dose family and the 2-dose family

[redacted]

(at-least-2-dose/only-2-dose), after primary objectives are met. Furthermore, within each family, the endpoints will be evaluated sequentially; that is, the subsequent endpoint is evaluated only if the criteria are met for the previous endpoints.

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).

Day 1 is considered to be the date the subject receives his or her first vaccination. There is no screening period in this study; therefore, Day -1 is not applicable.

Except for the primary and secondary endpoints for VE evaluations, all CIs for proportions will be 2-sided 95% intervals obtained using the exact Clopper-Pearson method as described by Agresti.[2]

A descriptive table will be included that will list the total number of diarrheal episodes that met clinical criteria for a potential CDI case and how many were excluded from analysis (with the reason for exclusion), overall and in each study group.

5.2.1. Analyses for Binary Data

5.2.1.1. Efficacy Data

CDI incidence will be calculated based on the various case definitions as defined in Section 3.4.

The incidence of a case occurring according to the specific definition is defined as:

= 1 if the CDI event meets the case definition

= 0 if the CDI event does not meet the case definition

CCI [redacted] Table 10 displays the derived variables of whether or not a CDI event meets each definition.

[redacted]

Table 10. Derived Variables for CDI Case Definitions

Timing of CDI Event	Definition 1 Yes (1)	Definition 2 Yes (1)	CCI	CCI
No previous CDI onset in the prior 8 weeks	If diarrhea is present and sample is positive for toxin B gene (via PCR) AND positive for toxin A and/or toxin B via central laboratory analysis			
No previous CDI onset in the prior 8 weeks	Diagnosed pseudomembranous colitis AND sample is positive for toxin B gene (via PCR) via central laboratory analysis			
Previous CDI onset within 8 weeks before current CDI episode		If diarrhea is present and sample is positive for toxin B gene (via PCR) AND positive for toxin A and/or toxin B via central laboratory analysis		
Previous CDI onset within 8 weeks before current CDI episode		Diagnosed pseudomembranous colitis AND sample is positive for toxin B gene (via PCR) via central laboratory analysis		

Abbreviations: CDI = *Clostridium difficile* infection; PCR = polymerase chain reaction.

Furthermore, the incidence of each CDI event that meets a CDI case definition and timing of when the event occurred in relation to vaccination will be defined as shown in Table 11. All CDI events that meet a case definition will have the timing of occurrence derived.

Table 11. Derived Variables for Timing of CDI Case Occurrence

Timing of CDI Case Occurrence	Yes (1)
Immediately after receipt of third dose of investigational product onwards.	CDI case was reported any time after receipt of the third dose. Date of case ≥ date of third vaccination.
14 Days after receipt of third dose of investigational product onwards.	CDI case was reported at least 14 days after receipt of the third dose. Date of case ≥ date of third vaccination + 14 days.

Table 11. Derived Variables for Timing of CDI Case Occurrence

Timing of CDI Case Occurrence	Yes (1)
Immediately after receipt of second dose of investigational product onwards.	CDI case was reported from any time after receipt of the second dose. Date of case ≥ date of second vaccination.
14 Days after receipt of second dose of investigational product onwards.	CDI case was reported at least 14 days after receipt of the second dose. Date of case ≥ date of second vaccination + 14 days.
Immediately after receipt of second dose of investigational product and before third dose of investigational product.	CDI case was reported from any time after receipt of the second dose to before receipt of the third dose for subjects who received a third dose or 168 days after the second dose for subjects who did not receive the third dose. Date of the second vaccination ≤ date of case < date of third vaccination (actual or expected: date of Dose 2 + 168 days).
14 Days after receipt of second dose of investigational product and before third dose of investigational product.	CDI case was reported at least 14 days after receipt of the second dose to before receipt of the third dose for subjects who received a third dose or 168 days after the second dose for subjects who did not receive the third dose. Date of the second vaccination + 14 days ≤ date of case < date of third vaccination (actual or expected: date of Dose 2 + 168 days).

Abbreviation: CDI = *Clostridium difficile* infection.

In addition to this, subject-level variables for each endpoint indicating if endpoint criteria described in Table 13 through Table 20 have been met will be derived. The following binary definitions apply for subjects for each endpoint:

= 1 if the subject has a CDI case that meets the specific endpoint,

= 0 if the subject has no CDI case that meets the specific endpoint,

= <empty> endpoint is not applicable for the subject or insufficient data are available for derivation.

Although subjects may have several CDI cases, most of the efficacy endpoints require subjects to provide only 1 observation to meet the requirements of the endpoint. Examples of these endpoints are those associated with the study's primary efficacy objective. For these endpoints, the first case meeting the specific endpoint will be flagged as 1, and all other cases will be flagged as 0. There are other endpoints that look at the accumulation of multiple cases within a subject. Examples of these endpoints are those associated with the secondary efficacy objective such as "all episodes of CDI as defined by case definitions 1 and 2" CCI CCI [redacted] For these, within a subject, all cases meeting the criteria will be flagged as 1, and all other cases will be flagged as 0.

[redacted]

5.2.1.2. Safety Data

All of the primary safety endpoints, including proportions of subjects reporting local reactions, systemic events, AEs, and SAEs, will be summarized with percentages and the exact 2-sided 95% CIs by vaccine group.

For tier 1 and tier 2 AEs, the difference in the percentages between *C difficile* vaccine and placebo will be provided. The Miettinen and Nurminen (1985)[3] method will be used to derive the 95% CI for the risk difference between vaccine and placebo. The p-value from the Miettinen and Nurminen method will also be provided for tier 1 events.

The exact CI for a proportion will be computed using the F distribution. If *r* equals the number of responses and *n* equals the number of subjects, 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

$$p_L = \frac{rF_L}{(rF_L + (n - r + 1))} \quad \text{and} \quad p_U = \frac{(r+1)F_U}{(n-r) + (r+1)F_U}$$

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 should be set equal to 1.0 so P_L equals 0. When r equals n, F_U should be set equal to 1.0 so p P_U equals 1. The CI using the F distribution is described in Collett (1991).[4]

5.2.2. Analyses for Continuous Data

5.2.2.1. 1000 Person-Years and Infection Rate Ratio

CDI incidence per 1000 person-years will be calculated for each vaccine group (*C difficile* vaccine and placebo) at various time periods and for each specified endpoint. The number of CDI cases occurring during a specific time period (derived in Section 5.2.1.1) among all subjects in a given vaccine group and population will be divided by the cumulated number of postvaccination surveillance days, adjusted for year and multiplied by 1000.

Example for first primary case:

Assume that 7100 subjects in the placebo group (90% of the initial planned enrollment for placebo group) received the third dose and are included in the mITT-3 population. Eighty-five (85) of these subjects have a primary CDI case (~1.2% attack rate) after the third dose was administered. The number of days from after the third vaccination to the end of the study will be calculated for each subject who did not experience a given endpoint. The number of days from after the third vaccination to the beginning of the endpoint case will be calculated for each subject who did experience the endpoint. These durations will be summed and included as the denominator.

[redacted]

For purposes of this example, assume a 6-month surveillance period identifying each subject who did not achieve the endpoint, which yields 180 days of subject-level surveillance after the subject's third dose. Also, assume all subjects who did achieve the endpoint did so 10 days after the third dose, yielding 10 days of subject-level surveillance. The total cumulative days of surveillance would be ([7100 - 85] × [180] + [85 × 10]) = 1,263,550 days.

The total cumulative person-days are 1,263,550, which are adjusted for 1 year, therefore dividing by 365.25.

CDI incidence per 1000 person-years is (85 / [1,263,550 / 365.25]) × 1000 = 24.57

The interpretation is such that 24.57 first primary CDI cases would be expected per 1000 persons observed for 1 year after the third vaccination for subjects who received placebo and who were in the mITT-3 population.

Example for first recurrent case:

Assume that 7100 subjects in the placebo group (90% of the initial planned enrollment for the placebo group) received the third dose and are included in the mITT-3 population. Forty-five (45) subjects had a total of 48 recurrent CDI cases after the third dose was administered, where 1 subject had 3 recurrent CDIs at Days 20, 30, and 70; and another subject had 2 recurrent CDIs at Days 15 and 40. The number of days from after the third vaccination to the end of the study will be calculated for each subject who did not experience a given endpoint. The number of days from after the third vaccination to the beginning of the endpoint case of the first recurrent case will be calculated for each subject who did experience the endpoint. These durations will be summed and included as the denominator. For purposes of this example, assume a 6-month surveillance period identifying each subject who did not achieve the endpoint, which yields 180 days of subject-level surveillance after the third dose. Also, assume all subjects who did achieve the endpoint did so 30 days after the third dose, yielding 30 days of subject-level surveillance. The total cumulative days of surveillance would be ([7100 - 45] × [180] + [43 × 30] + [1 × 20] + [1 × 15]) = 1,271,225 days.

The total cumulative person-days are 1,271,225, which are adjusted for 1 year, therefore dividing by 365.25.

CDI incidence per 1000 person-years is (45 / [1,271,215 / 365.25]) × 1000 = 12.93

The interpretation is such that 12.93 first recurrent CDI cases would be expected per 1000 persons observed for 1 year after the third vaccination for subjects who received placebo and who were in the mITT-3 population.

Example for all cases:

Several endpoints involve assessing the incidence of all CDI cases.

[redacted]

Assume that 7100 subjects in the placebo group (90% of the initial planned enrollment for the placebo group) received the third dose and are included in the mITT-3 population. Eighty-five (85) of these subjects have a primary CDI case after the third dose was administered and 45 of these subjects have a total of 48 recurrent cases after the primary case.

Since we are looking for any and all cases within each subject, each subject's surveillance time would not stop upon observation of a case. For purposes of this example, assume a 6-month surveillance period for all subjects, which yields 180 days of subject-level surveillance after their third dose. The total cumulative days of surveillance would be (7100 × 180) = 1,278,000 days.

The total cumulative person-days are 1,278,000, which are adjusted for 1 year by dividing by 365.25.

CDI incidence per 1000 person-years is ([85 + 48] / [1,278,000 / 365.25]) × 1000 = 38.01

The interpretation is that 38.01 cases would be expected per 1000 persons observed for 1 year after the third vaccination for subjects who received placebo and who were in the mITT-3 population.

CDI incidence per 1000 person-years will be assessed during the following time periods. The paragraphs below the time periods present examples to count the start and end dates for each case in the mITT populations. Similar derivations for 14 days after vaccination will also be computed for the PP-2 and PP-3 populations.

- After receipt of the third dose of investigational product onwards

    - CDI cases reported after receipt of the third dose and cumulative person-time in days defined as the number of days from after the third vaccination to the time of the case, end of the study, study withdrawal or discontinuation, or when the subject had a major protocol violation (for PP endpoints), whichever occurs first.

- After receipt of the second dose of investigational product onwards

    - CDI cases reported after receipt of the second dose and cumulative person-time in days defined as the number of days from after the second vaccination to the time of the case, end of the study, study withdrawal or discontinuation, or when the subject had a major protocol violation (for PP endpoints), whichever occurs first.

- After receipt of the second dose of investigational product and before receipt of the third vaccination

    - For subjects who receive a third vaccination of investigational product, CDI cases reported between Vaccination 2 and Vaccination 3 and cumulative person-time in days defined as days between Vaccination 2 and Vaccination 3, time of the case if the case occurs prior to Vaccination 3, end of the study surveillance period, study

[redacted]

withdrawal or discontinuation, or when a subject had a major protocol violation (for PP endpoints), whichever occurs first.

- For subjects who do not receive a third vaccination of investigational product, cumulative person-time is defined as days between Vaccination 2 and time of the case if the case occurs prior to the estimated time of Vaccination 3 (latest visit window timing for Visit 4, 168 days after the date of Vaccination 2), end of the study surveillance period, study withdrawal or discontinuation, or when a subject had a major protocol violation (for PP endpoints), whichever occurs first.

- After receipt of the first dose of investigational product onwards

  - CDI cases reported after receipt of the first dose and cumulative person-time in days defined as the number of days from after the first vaccination to the time of the case, end of the study, or study withdrawal or discontinuation, whichever occurs first.

The infection rate ratio (IRR) will be calculated as:

(CDI incidence rate per 1000 person-years for the *C difficile* vaccine group) / (CDI incidence rate per 1000 person-years for the placebo group)

5.2.2.2. Vaccine Efficacy

Vaccine efficacy (VE) and associated 2-sided CIs will be provided separately for evaluating efficacy of 2 and 3 doses of *C difficile* vaccine in reducing CDI incidence categorized using multiple case definitions.

For endpoints involving the identification of 1 case per subject, VE is defined as a percentage: VE = 100 × (1 - IRR). The 2-sided adjusted CI will be derived using the following methodology (Nauta).[5]

Under the assumption that the numbers of cases in both vaccine groups, s_1 and s_0 for *C difficile* cases and placebo cases, respectively, follow a Poisson distribution with parameter λ_1 (incidence rate) for the *C difficile* vaccine group and λ_0 for the placebo group, we can assume that s_1 is binomially B(s,π) distributed, conditional on s, the total number of cases, and with

$$\pi = T_1 \lambda_1 / (T_1 \lambda_1 + T_0 \lambda_0)$$

where T_i represents total person-time for each vaccine group (i = 0, 1), and π represents the adjusted infected case rate for the *C difficile* vaccine group.

Then the test of null hypothesis of VE ≤20% is equivalent to test H_0: $\lambda_1 \geq 0.8\lambda_0$ and exact confidence limits for π are translated to exact confidence limits for λ_1/λ_0, which is the estimate of IRR, and for estimated VE = 1 - IRR. The 2-sided CIs for π will be calculated using the Clopper-Pearson method and used in developing the CI for VE. Formulas are as follows where r is the ratio of total person-time between the *C difficile* and placebo groups:

[redacted]

$$LCL_{\lambda_1/\lambda_0} = \frac{LCL_\pi}{r(1 - LCL_\pi)} \; and \; UCL_{\lambda_1/\lambda_0} = \frac{UCL_\pi}{r(1 - UCL_\pi)}$$

where LCL is the lower confidence limit and UCL is the upper confidence limit. Exact lower and upper 100(1 - α)% confidence limits for VE are:

$$LCL_{VE} = 1 - UCL_{\lambda_1/\lambda_0} \; and \; UCL_{VE} = 1 - LCL_{\lambda_1/\lambda_0}$$

There are several secondary efficacy endpoints involving the identification of more than 1 case per subject. These endpoints are as follows:

- All episodes of CDI as defined by case definitions 1 and 2.
- All episodes of CDI as defined by case definitions 1 through 4.

For these endpoints, VE and the corresponding confidence limits will be computed using a proportional means model via PHREG procedure in SAS (Johnston and So).[6]

5.2.2.3. Duration and Difference in Means

All durations calculated for purposes of endpoint analysis will be derived as:

(resolution date – date it first occurred) + 1

Note: Resolution date is the end date.

Cases that do not have a resolution date will have an undefined duration.

Means will be calculated for such durations and the difference in means for endpoint durations (ie, time to resolution of a first primary CDI episode [meeting definition 1], days in hospital, etc) between vaccine groups will be calculated using a Student's t distribution. Two-sided CIs will also be computed and follow the formula where M_i is the mean for each vaccine group (i = 0, 1), $t_{\alpha/2,n-1}$ is the desired α level of confidence [2-sided], and S_{M1-M0} is the estimated standard error of the difference in means.

$$CI = M_1 - M_0 \pm (t_{\alpha/2,n-1})(S_{M1-M0})$$

The difference in means and the 2-sided CIs for continuous endpoint analysis will be performed also using the Student's t distribution.

If there are outliers, the Wilcoxon rank sum test may be conducted as well.

[redacted]

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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 following the Safety Rulebook Summary developed by Pfizer.

5.3.1.1. Reactogenicity Data

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

The reactogenicity data are collected through the e-diary, which does not allow subjects to skip the question. Therefore, for a specific day, as long as the e-diary data are transferred for that day, all of the reactogenicity data for the subject on that day are nonmissing. The e-diary transmission and completion status will be summarized per Section 3.8.1. The e-diary completion summary will provide the missing data information on the reactogenicity data.

Based on data from available studies, the missing data on reactogenicity are minimal, which is consistent with Li et al (2011).[8] No sensitivity analysis is planned for reactogenicity data.

6. ANALYSIS AND SUMMARIES

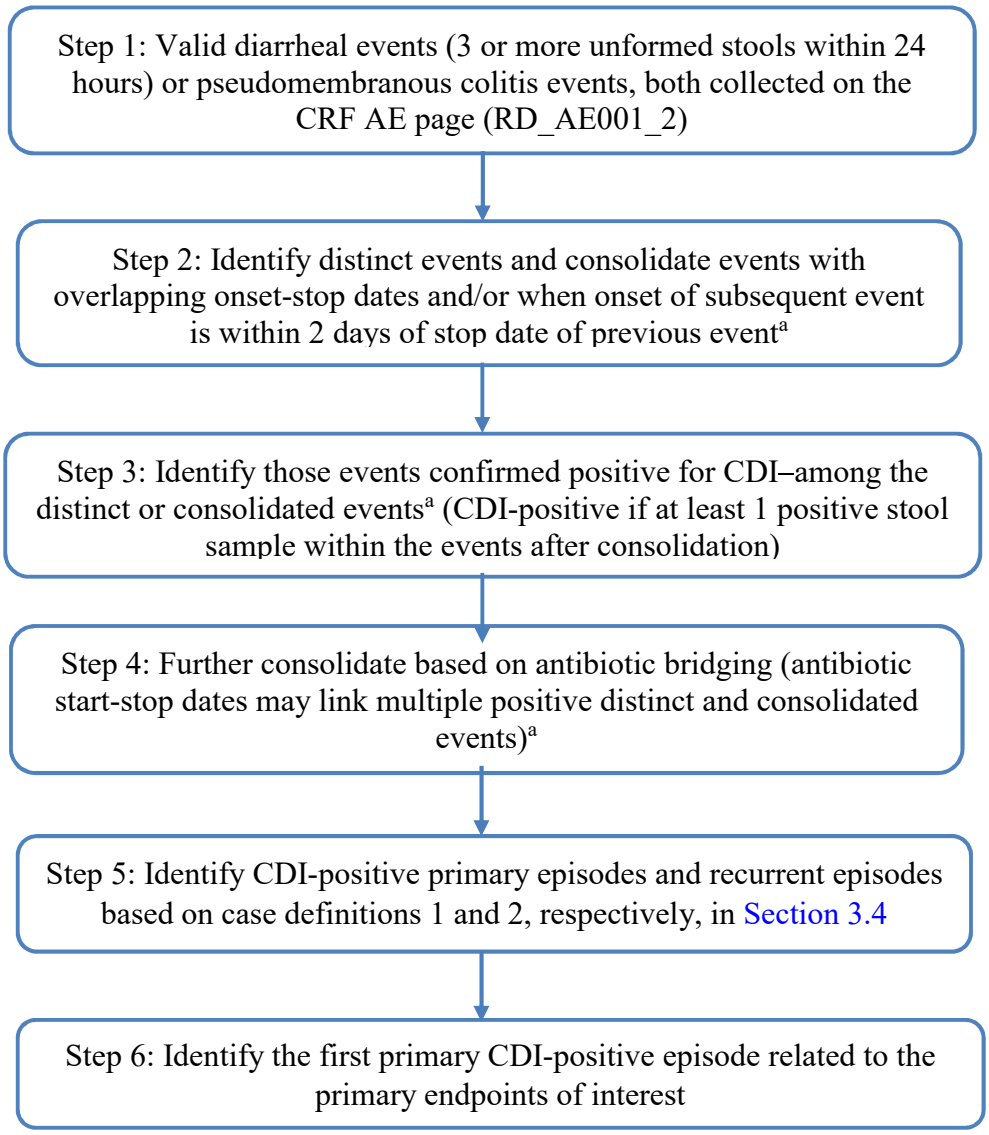
Data captured on the CRF and derived for study endpoints will be included in data listings accordingly.

6.1. Primary Endpoints

6.1.1. Primary Efficacy Endpoints

The primary efficacy endpoints are derived according to a case identification algorithm represented in the subject-level flowchart below.

[redacted]



a. An event (episode) will be considered to have resolved once there have been at least 2 days without passage of 3 or more unformed stools (Bristol stool chart types 5-7). The antibiotic bridging rule will apply when there are multiple CDI-positive events in close proximity for the same subject.

More detail on this process will be provided in the programming specifications.

The primary efficacy endpoints will be descriptively summarized in terms of total number of cases reported, number of subjects available in the population, number of 1000 person-years, and the infection rate by vaccine group. The VE point estimate and the type I adjusted CI for VE will be calculated for each endpoint (Table 13).

[redacted]

Table 13. Interim Analysis 1, 2, and 3 for Primary Objective – Vaccine Efficacy

Objective	Case Definition	Time Period for Case Accrual	Analysis Population	Primary Efficacy Endpoint	Null Hypothesis	Type I Error (1-Sided)	Success Criterion
VE in reducing the incidence of first primary CDI	1	14 days after Dose 3 to end of surveillance period	PP-3	CDI incidence of a first primary episode per 1000 person-years of follow-up	H_{03} $VE_3 \leq 20\%$	0.006 for IA1 and IA2, 0.009 for IA3	LL of CI (98.8% for IA1 and IA2, 98.2% for IA3) for VE >20%

Abbreviations: CDI = *Clostridium difficile* infection; LL = lower limit; PP = per-protocol; VE = vaccine efficacy.

A decision to stop the trial based on efficacy will be made at interim analysis 1, 2 or interim analysis 3 using only H_{03} and the first 30, 40 or 50 consecutive cases. (A decision may also be made to stop the trial because of futility after each interim analysis.) If the trial is stopped at interim analysis 1, interim analysis 2, or interim analysis 3 because of efficacy, the additional primary endpoints will be analyzed as shown in Table 14 and Table 15.

Table 14. Final Analysis if Trial Stopped at Interim Analysis 1, 2, or 3 Because of Efficacy for Primary Objective for Per-Protocol Population – Vaccine Efficacy

Objective	Case Definition	Time Period for Case Accrual	Analysis Population	Primary Efficacy Endpoint	Null Hypothesis[a]	Type I Error (1-Sided)	Success Criterion
VE in reducing the incidence of first primary CDI	1	14 days after Dose 2 to end of surveillance period	PP-2	CDI incidence of a first primary episode per 1000 person-years of follow-up	H_{02} $VE_2 \leq 20\%$	0.018 for IA1, IA2, and IA3	LL of CI (96.4% for IA1, IA2, and IA3) for VE >20%

Abbreviations: CDI = *Clostridium difficile* infection; LL = lower limit; PP = per-protocol; VE = vaccine efficacy.

a. H_{02} will be evaluated if H_{03} for PP-3 is rejected.

[redacted]

Table 15. Final Analysis if Trial Stopped at Interim Analysis 1, 2, or 3 Because of Efficacy for Primary Objective for Modified Intent-to-Treat Populations (Point Estimate and CI)

Objective	Case Definition	Time Period for Case Accrual	Analysis Population	Primary Efficacy Endpoint	Type I Error (1-Sided)	Parameter for Primary Efficacy Endpoint
VE in reducing the incidence of first primary CDI	1	Day of Dose 3 to end of surveillance period	mITT-3	CDI incidence of a first primary episode per 1000 person-years of follow-up	0.018 for IA1, IA2, and IA3	LL of CI (96.4% for IA1, IA2, and IA3) for VE >20%
VE in reducing the incidence of first primary CDI	1	From 14 days after receipt of third dose of investigational product onwards	mITT-3	CDI incidence of a first primary episode per 1000 person-years of follow-up	0.018 for IA1, IA2, and IA3	LL of CI (96.4% for IA1, IA2, and IA3) for VE >20%
VE in reducing the incidence of first primary CDI	1	Day of Dose 2 to end of surveillance period	mITT-2	CDI incidence of a first primary episode per 1000 person-years of follow-up	0.018 for IA1, IA2, and IA3	LL of CI (96.4% for IA1, IA2, and IA3) for VE >20%
VE in reducing the incidence of first primary CDI	1	From 14 days after receipt of second dose of investigational product onwards	mITT-2	CDI incidence of a first primary episode per 1000 person-years of follow-up	0.018 for IA1, IA2, and IA3	LL of CI (96.4% for IA1, IA2, and IA3) for VE >20%

Abbreviations: CDI = *Clostridium difficile* infection; PP = per-protocol; VE = vaccine efficacy.
Note: Analyses of all mITT populations will be performed to complement PP analyses.

As of the PACL dated 02 Dec 2021, the final analysis will be conducted with all of the available data, and the primary endpoints will be analyzed for the PP-3–related analysis of H_{03}, as shown in Table 16 and Table 17.

Table 16. Final Analysis for Primary Objective for Per-Protocol Populations – Vaccine Efficacy

Objective	Case Definition	Time Period for Case Accrual	Analysis Population	Primary Efficacy Endpoint	Null Hypothesis[a]	Type I Error (1-Sided)	Success Criterion
VE in reducing the incidence of first primary CDI	1	14 days after Dose 3 to end of surveillance period	PP-3	CDI incidence of a first primary episode per 1000 person-years of follow-up	H_{03} $VE_3 \leq 20\%$	0.018	LL of 96.4% CI for VE >20%

[redacted]

Table 16. Final Analysis for Primary Objective for Per-Protocol Populations – Vaccine Efficacy

Objective	Case Definition	Time Period for Case Accrual	Analysis Population	Primary Efficacy Endpoint	Null Hypothesis[a]	Type I Error (1-Sided)	Success Criterion
VE in reducing the incidence of first primary CDI	1	14 days after Dose 2 to end of surveillance period	PP-2	CDI incidence of a first primary episode per 1000 person-years of follow-up	H_{02} $VE_2 \leq 20\%$	0.018	LL of 96.4% CI for VE >20%

Abbreviations: CDI = *Clostridium difficile* infection; LL = lower limit; PP = per-protocol; VE = vaccine efficacy.

a. H_{02} will be evaluated if H_{03} for PP-3 is rejected.

Table 17. Final Analysis for Primary Objective for Modified Intent-to-Treat Populations (Point Estimate and CI)

Objective	Case Definition	Time Period for Case Accrual	Analysis Population	Primary Efficacy Endpoint	Type I Error (1-Sided)	Parameter for Primary Efficacy Endpoint
VE in reducing the incidence of first primary CDI	1	Day of Dose 3 to end of surveillance period	mITT-3	CDI incidence of a first primary episode per 1000 person-years of follow-up	0.018	LL of 96.4% CI for VE >20%
VE in reducing the incidence of first primary CDI	1	From 14 days after receipt of third dose of investigational product onwards	mITT-3	CDI incidence of a first primary episode per 1000 person-years of follow-up	0.018	LL of 96.4% CI for VE >20%
VE in reducing the incidence of first primary CDI	1	Day of Dose 2 to end of surveillance period	mITT-2	CDI incidence of a first primary episode per 1000 person-years of follow-up	0.018	LL of 96.4% CI for VE >20%
VE in reducing the incidence of first primary CDI	1	From 14 days after receipt of second dose of investigational product onwards	mITT-2	CDI incidence of a first primary episode per 1000 person-years of follow-up	0.018	LL of 96.4% CI for VE >20%

Abbreviations: CDI = *Clostridium difficile* infection; PP = per-protocol; VE = vaccine efficacy.

Note: Analyses of all mITT populations will be performed to complement PP analyses.

[redacted]

6.1.2. Primary Safety Endpoints

Safety endpoint data will be summarized according to vaccine received. The safety population at each corresponding dose will be used for the analysis for each vaccination.

6.1.2.1. Local Reactions and Systemic Events

The derived variables for each local reaction, systemic event, any local reaction, and any systemic event (ie, swelling, redness, pain at the injection site, fever, vomiting, headache, fatigue, new or worsening muscle pain, new or worsening joint pain, any local reaction, any systemic event) occurring on CCI any day during Day 1 to Day 7 following vaccination will be summarized. The number and percentage of subjects reporting a reaction/event on each day and on any day and the associated 95% Clopper-Pearson CIs will be displayed for each vaccine group.

The presence and maximum severity of each reaction/event and any reaction/event within 7 days (over all days [Days 1-7]) after vaccination will be summarized through proportions of subjects, percentages, and associated 95% Clopper-Pearson CIs.

For each local reaction and systemic event, the maximum duration of each reaction/event will be descriptively summarized by vaccine group. Only subjects experiencing the reaction/event will be included in the analysis. The onset day of each reaction/event will also be summarized for each vaccine group.

All of the above data summaries will be displayed for each vaccination by vaccine group as well as after any vaccination for the presence on each day and maximum severity endpoints.

An overall listing of reactogenicity data and a separate listing of all severe and Grade 4 local reactions and systemic events will be provided.

6.1.2.2. Adverse Events and Serious Adverse Events

The number and percentage of subjects experiencing at least 1 AE/SAE and the number of events will be descriptively summarized by vaccine group for the overall safety population.

Tier 1 and tier 2 events, as defined in Section 3.7.1, will present the proportion of AEs observed in each vaccine group along with the point estimates and associated 95% CIs of the risk difference (the difference of incidence rates) between *C difficile* vaccine and placebo. For both tier 1 and tier 2, the 95% CIs will be calculated using the Miettinen and Nurminen method described in Section 5.2.1.2. The p-value from the Miettinen and Nurminen method will be presented for tier 1 events only.

AE and SAE displays will be sorted in descending order of point estimates of risk difference within system organ class.

Separate listings of AEs and SAEs will also be provided.

[redacted]

6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be analyzed only at the final analysis. All VEs will be estimated using the same method as done for the primary efficacy endpoints, with adjusted type I error. Case-level variables for each endpoint have been defined in Section 5.2.1.1.

The analyses for the secondary objectives are outlined in Table 18 and the evaluable and mITT population will be used for the analysis. The assessment criteria for the secondary objective evaluation are listed below:

- For evaluating *C difficile* vaccine in reducing the incidence of CDI cases (VE analysis), the lower limit (LL) of 98.2% CI for VE >0.
- For evaluating the efficacy of Pfizer's *C difficile* vaccine in reducing the severity of CDI in terms of the duration, the upper limit (UL) of 2-sided 98.2% CI < 0 for the difference in mean duration of CDI between the *C difficile* vaccine group and the placebo group *(C difficile* vaccine group – placebo group).
- For evaluating the efficacy of Pfizer's *C difficile* vaccine in reducing the severity of CDI in terms of the risk ratio, the UL of 2-sided 98.2% CI < 1.0 for the ratio of the proportion of subjects experiencing CDI who have a non–protocol-related medically attended visit in the *C difficile* vaccine group to the proportion of the subjects in the placebo group.

Table 18. Final Analysis for Secondary Objectives – Vaccine Efficacy (Point Estimate and 98.2% CI)

Objective	Case Definition	Time Period for Case Accrual	Analysis Population(s)	Parameter for Secondary Efficacy Endpoint
3-Dose Family (assessments will be done sequentially)				
VE in reducing the incidence of all CDI cases	1 and 2	14 days after Dose 3 to end of surveillance period/Day of Dose 3 to end of surveillance period	PP-3/mITT-3	Incidence of CDI as defined by case definitions 1 and 2
VE in reducing the severity of CDI	1	14 days after Dose 3 to end of surveillance period/Day of Dose 3 to end of surveillance period	PP-3/mITT-3	Mean and median time to resolution of case in subjects who had first primary episodes of CDI and difference in mean time to resolution
VE in reducing the severity of CDI	1	14 days after Dose 3 to end of surveillance period/Day of Dose 3 to end of surveillance period	PP-3/mITT-3	Proportion and ratio of proportions of required non–protocol-related medical attention/visits in subjects who had first primary episodes of CDI from *C difficile* vaccine group and placebo group

[redacted]

Table 18. Final Analysis for Secondary Objectives – Vaccine Efficacy (Point Estimate and 98.2% CI)

Objective	Case Definition	Time Period for Case Accrual	Analysis Population(s)	Parameter for Secondary Efficacy Endpoint
VE in reducing the incidence of recurrent CDI	2	14 days after Dose 3 to end of surveillance period/Day of Dose 3 to end of surveillance period	PP-3/mITT-3	Incidence of recurrent CDI as defined by case definition 2
At-Least-2-Dose/Only-2-Dose Family (assessments will be done sequentially)				
VE in reducing the incidence of all CDI cases	1 and 2	14 days after Dose 2 to end of surveillance period/Day of Dose 2 to end of surveillance period	PP-2/mITT-2	Incidence of CDI as defined by case definitions 1 and 2
VE in reducing the incidence of recurrent CDI	2	14 days after Dose 2 to end of surveillance period/Day of Dose 2 to end of surveillance period	PP-2/mITT-2	Incidence of recurrent CDI as defined by case definition 2
VE in reducing the incidence of primary CDI	1	14 days after Dose 2 to end of surveillance period before Dose 3[a]/Day of Dose 2 to end of surveillance period before Dose 3[a]	PP-2/mITT-2	Incidence of first primary CDI as defined by case definition 1
VE in reducing the incidence of recurrent CDI	2	14 days after Dose 2 to end of surveillance period before Dose 3[a]/Day of Dose 2 to end of surveillance period before Dose 3[a]	PP-2/mITT-2	Incidence recurrent CDI as defined by case definition 2

Abbreviations: CDI = *Clostridium difficile* infection; PP = per-protocol; VE = vaccine efficacy.
Note: All evaluations will be performed as detailed above. Interpretation of results will follow a staged approach dependent on success of the preceding evaluation. Evaluation order will apply to both the 3-dose family and the at-least-2-dose/only-2-dose family.

a. End of surveillance period before Dose 3 is the day of the third dose or the day the third dose was expected (168 days after Dose 2) for subjects who received only 2 doses.

For the analysis of multiple events, the mean cumulative function (MCF) for number of events will be estimated by the proportional means model (PROC PHREG procedure from SAS) to compute the regression parameter estimates by maximizing a partial likelihood.[6] Then the VE will be estimated by 1 minus the estimated hazard ratio.

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6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct

6.5.1.1. Subject Disposition, Vaccination Administration, and Blood Samples

The number and percentage of subjects who are randomized will be included in the disposition summary. Screen failures and reasons for screen failure may be included in a separate tabulation.

Subjects who received each vaccination and who are included in each study population (safety; mITT-1 through mITT-3; PP-2 and PP-3) will be summarized. Subjects completing the study as well as those who withdrew during the vaccination phase, who completed the vaccination phase, and who withdrew prior to the end of the study will be reported along with the reasons for withdrawal.

For each blood draw, the numbers and percentages of subjects randomized, vaccinated at each visit (Visits 1, 2, and 4), and providing blood samples within the protocol-specified time frame, as well as before and after the specified time frame, will be tabulated.

Summary tables will be presented for each randomized vaccine group and total population.

Listings will be provided for the following:

- Subjects' noncompliant vaccine administration
- Protocol violations
- Subjects receiving the vaccine not as randomized
- Subjects receiving vaccine who were not randomized
- Subjects with temporary delays to vaccine administration
- Subjects who withdrew from the study and reasons for withdrawal
- Subjects who withdrew because of AEs
- Subjects included or excluded from each analysis population and reasons for exclusion

6.5.1.2. Demographic, Medical History, and Baseline Characteristics

Variables defined in Section 3.8.2 will be reported according to Pfizer standard summary reporting. Summaries will be provided for each vaccine group separately. Demographic and baseline characteristic summaries may also be generated for different analysis sets as defined in Section 4.

Medical history reports will be provided by vaccine group.

6.5.2. E-Diary Completion

E-diary compliance as defined in Section 3.8.1 will be summarized for each dose by vaccine group and total compliance using descriptive statistics. The safety population will be used to generate the summary reports. The denominator for the e-diary compliance rates will be the total number of subjects who received the specific vaccination.

6.5.3. Nonstudy Vaccine and Concomitant Medications

Nonstudy vaccines and concomitant medications captured throughout the study will be descriptively summarized for subjects in the overall safety population.

6.6. Analysis for Other Safety Endpoints

All safety data will be summarized according to vaccine received. The safety population will be used for the analysis. The percentage of subjects reporting the defined events will be summarized with exact 2-sided 95% CIs by vaccine group.

6.6.1. Physical Examinations and Vital Signs

Physical examinations and vital signs may be recorded on the CRF prior to receiving the first dose of investigational product. Data listings will be provided in accordance with Pfizer reporting standards.

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6.6.2. Drug-Induced Liver Injury

For cases meeting the criteria of liver injury as defined in Section 8.4.2 of the study protocol, a listing will be provided.

6.7. Subgroup Analysis for Efficacy and Safety Endpoints

Subgroup analyses based on age category (see Table 2), race, ethnicity, and sex will be performed on all primary and secondary efficacy endpoints (as supplemental analysis) as well as the primary safety endpoints. Furthermore, supplemental analyses include region (North America; South America; Oceania; East Asia including Japan, South Korea, and Taiwan; Japan [by itself]; and Europe), comorbidity at baseline, healthcare exposure at baseline, and prior systemic antibiotic exposure will be performed on the primary and secondary efficacy endpoints.

The comorbidity subgroup will include subjects who have any of the following, which will be pooled together for analysis, at study entry:

1. Chronic lung disease (eg, chronic obstructive pulmonary disease [COPD], asthma, emphysema, chronic bronchitis)
2. Congestive heart failure
3. Inflammatory bowel disease
4. Renal disease
5. Diabetes
6. Deficiency anemia

The healthcare exposure subgroup will include the following prior or anticipated healthcare exposure and will be presented for each exposure risk separately:

1. Previous hospitalization
2. Outpatient visits (includes emergency room and healthcare provider)
3. Skilled nursing facilities or nursing home residence
4. Inpatient hospitalization >2 nights' duration scheduled >37 days after randomization

Additionally, categories based on 2 or more, 3 or more, and all of the above will be presented.

The prior systemic antibiotic exposure subgroup will include subjects who have received systemic (ie, oral or injected) antibiotics at any time in the 12 weeks prior to study entry.

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The above subgroup analyses will be performed on the mITT-3/mITT-2 population and are to be considered supportive assessments.

An additional supplemental analysis deriving VE and its 95% CI may be provided for the incidence of a first primary episode of CDI based on case definition 1 for subjects in the mITT-1 population.

Safety endpoints will be further described by race, age categories, and sex in a similar approach as discussed in Section 6.1.2.

7. INTERIM ANALYSES

7.1. Introduction

The following describes the plan that was in place for interim analyses prior to the PACL dated 02 Dec 2021. Three (3) planned formal interim analyses will be performed by the IST to assess whether there is overwhelming efficacy or futility with respect to the end-of-study success criterion. Each interim analysis result will confirm if the study will be stopped for efficacy or futility or if it will continue as planned (to reach 66 first primary CDI cases for the PP-3 population).

The first, second, and third interim analyses are planned after 30, 40, and 50 first primary CDI cases (by case definition 1 in Section 3.4.1) have occurred from 14 days after receipt of the third dose of investigational product in subjects meeting the PP-3 population definition. The cutoff date will be the calendar date of the confirmed 30, 40, or 50 cases. Only the primary efficacy endpoint will be examined.

As of the PACL dated 02 Dec 2021, the first interim analysis with 30 cases of first primary CDI was conducted as planned in protocol amendment 4. The recommendation from the E-DMC was to continue the study because the criteria to stop for efficacy or futility were not met. Due to operational futility, the study will be stopped and the final analysis will be performed with all the available data at study completion following the PACL.

The interim analysis efficacy results as well as the safety data will be presented to an unblinded E-DMC by the IST statistician. The IST will include statistician(s) and programmer(s) who are independent of the study team and who have unrestricted access to the true randomization assignments during the study. The IST will perform the statistical analysis for the interim analysis as well as the unblinded safety reviews and prepare the unblinded reports to be provided to the E-DMC members. The interim analysis will occur at the predefined time point; however, the E-DMC members may conduct additional meetings to review safety data at other time points during the study. The safety review meetings and related safety output will be detailed in the E-DMC charter.

7.2. Interim Analyses and Summaries

Prior to the PACL dated 02 Dec 2021, the following interim analyses and summaries were planned. At each interim analysis, the primary efficacy endpoint of H_{03}: VE ≤20% vs H_{a3}: VE >20% will be evaluated on the PP-3 population. The total number of cases reported, the number of subjects available in the population, the number of 1000 person-years, and the infection rate by vaccine group will be descriptively presented. The VE point estimate and the corresponding 2-sided 98.8% CI for interim analyses 1 and 2 and 98.2% CI for interim analysis 3 (adjusting for multiplicity as discussed in Section 5.1.4) will be calculated.

Hypothesis tests for H_{02} may be performed on the PP populations in a hierarchical fashion as described in Section 5.1.2 and will only be performed outside the context of the interim analysis meeting (ie, only information pertaining to H_{03} will be reviewed at interim analysis and serve as the basis for the decision to stop or to continue the trial).

The probabilities of stopping the trial for success are 44.3% at interim analysis 1 (ie, observe ≤6 cases in the *C difficile* vaccine group), 15.0% at interim analysis 2 (ie, observe ≤9 cases in the *C difficile* vaccine group), and 17.1% at interim analysis 3 (ie, observe ≤13 cases in the *C difficile* vaccine group) if the true VE is 70%.

Furthermore, safety data including reactogenicity, AEs, and SAEs reported will be summarized similarly as for the CSR and described in Section 6 of the SAP. Reporting will occur at defined time points outlined in the E-DMC charter as well as for the interim analysis.

Blinded summaries will be provided to the study team and unblinded summaries will be provided and presented to the E-DMC members at scheduled E-DMC meetings.

At each interim analysis, the conditional power of the study to reject the original null hypothesis, conditional upon the results accumulated so far, will be calculated. Futility may be declared and the study may cease enrollment, if the conditional power falls below the prespecified cutoff value. This futility analysis will be applied to the primary endpoint only, in the PP-3 efficacy population. Table 27 describes the statistical design operating characteristic modeling based on the modified study design.

The probabilities of stopping the trial because of futility are 6.6% at interim analysis 1 (ie, observe ≥11 cases in the *C difficile* vaccine group), 5.8% at interim analysis 2 (ie, observe ≥13 cases in the *C difficile* vaccine group), and 2.0% at interim analysis 3 (ie, observe ≥16 cases in the *C difficile* vaccine group) if the true VE is 70%.

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Table 27. Statistical Design Operating Characteristics

	Interim Analysis 1 (Total Cases = 30)		Interim Analysis 2 (Total Cases = 40)		Interim Analysis 3 (Total Cases = 50)		Final Analysis (Total Cases = 66)		
Vaccine Efficacy (%)	**Probability of Success (Cases in *C difficile* Vaccine Group ≤6)**	**Probability of Failure (Cases in *C difficile* Vaccine Group ≥11)**	**Probability of Success (Cases in *C difficile* Vaccine Group ≤9)**	**Probability of Failure (Cases in *C difficile* Vaccine Group ≥13)**	**Probability of Success (Cases in *C difficile* Vaccine Group ≤ 13)**	**Probability of Failure (Cases in *C difficile* Vaccine Group ≥16)**	**Probability of Success (Cases in *C difficile* Vaccine Group ≤20)**	**Probability of Failure (Cases in *C difficile* Vaccine Group ≥21)**	**Overall Probability of Success**
0	0.0007	0.9506	0.0002	0.0416	0.0003	0.0050	0.0002	0.0014	0.0014
20	0.0047	0.8512	0.0017	0.1066	0.0029	0.0211	0.0033	0.0085	0.0126
50	0.0838	0.4152	0.0397	0.2032	0.0721	0.0709	0.0739	0.0410	0.2696
60	0.2039	0.2146	0.0909	0.1490	0.1424	0.0557	0.1134	0.0300	0.5507
70	0.4427	0.0656	0.1496	0.0583	0.1711	0.0202	0.0845	0.0080	0.8479
80	0.7765	0.0067	0.1207	0.0063	0.0730	0.0015	0.0149	0.0003	0.9852

Note: Assumes equal follow-up times between vaccine groups.

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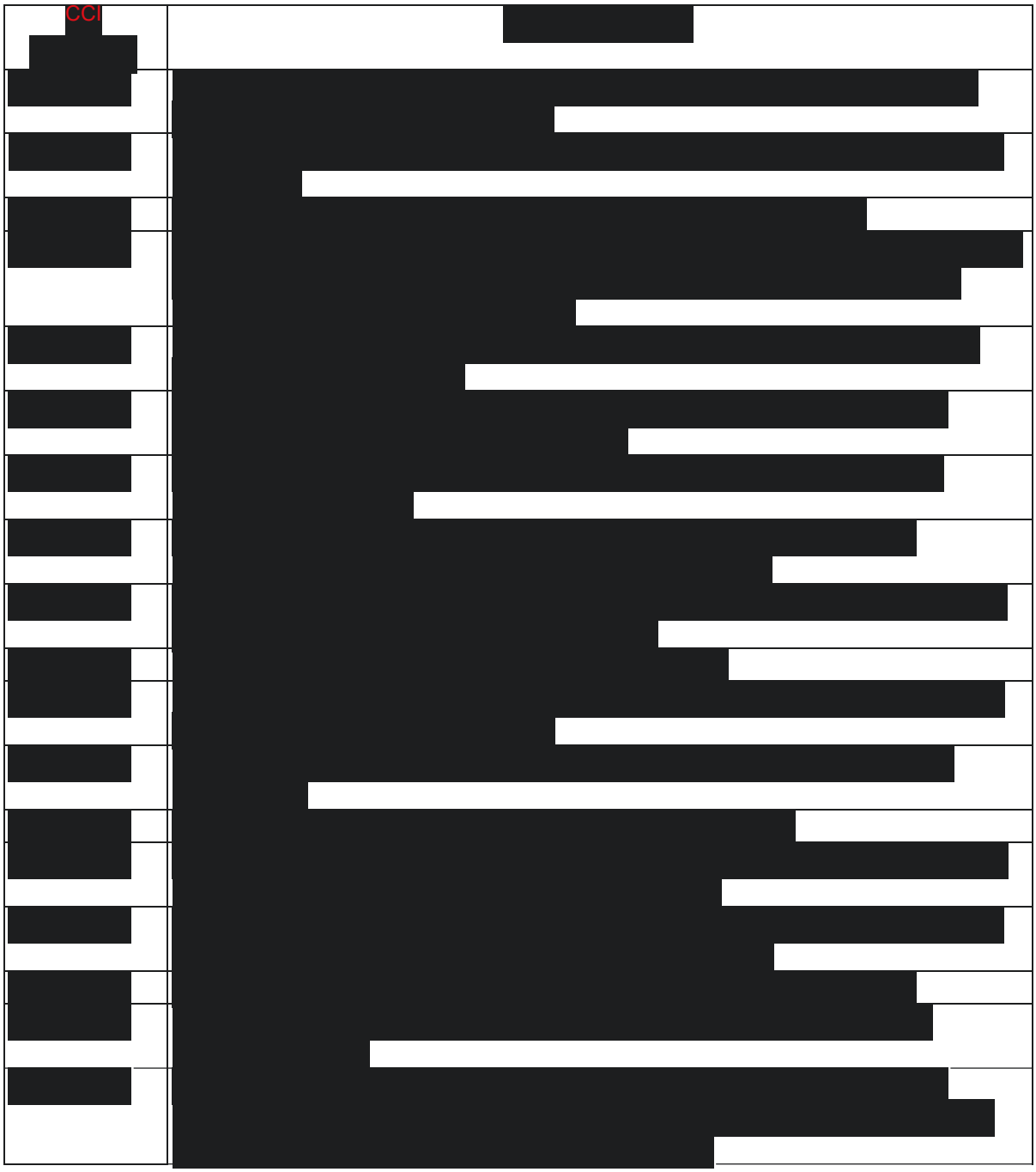


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