



**A PHASE 2, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLINDED  
STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND  
IMMUNOGENICITY OF TWO 3-DOSE REGIMENS OF A *CLOSTRIDIUM  
DIFFICILE* VACCINE IN HEALTHY ADULTS AGED 65 TO 85 YEARS**

**Compound:** PF-06425090

**Compound Name:** *Clostridium difficile* vaccine

**US IND Number:** 15150

**Protocol Number:** B5091009

**Phase:** 2

**Document History**

<b>Document</b>	<b>Version Date</b>	<b>Summary of Changes and Rationale</b>
Amendment 2	04-April-2017	<p>Added an optional additional blood draw of 20 mL to 50 mL of whole blood at Visit 12 for subjects enrolled in the extension stage (month regimen) at designated sites. Several changes were made throughout this protocol amendment to adjust blood volumes collected at Visit 12 and to modify language in order to allow whole blood sample testing for exploratory purposes. Additional exploratory analyses will be performed on study samples to augment vaccine assay development. Changes were made to the following sections:</p> <ul style="list-style-type: none"><li>• Schedule of Activities (Schedule of Activities for Subjects Participating in the Extension Stage)</li><li>• Study Procedures, Section 6.3.4 (Visit 12: Month 6 After Vaccination 4 [<math>\pm 30</math> Days])</li><li>• Assessments, Section 7.2 (Immunogenicity)</li></ul>

Amendment 1	11-April-2016	<p>Added an extension stage to the study: This will include subjects in both dosing regimens who received the first 3 doses of <i>C difficile</i> vaccine (not placebo). Subjects in the extension stage will receive a fourth dose of <i>C difficile</i> at the same antigen dose level (100 µg or 200 µg) as they received previously or placebo, approximately 1 year after their third dose. The subjects in the extension stage will be followed for a further 3 years (visits approximately every 6 months) to assess antibody persistence.</p> <p>Added objectives and endpoints for the extension stage.</p> <p>Added eligibility criteria for the extension stage.</p> <p>Added an unblinding step for subjects in the original portion and extension stages of the study.</p> <p>Added a schedule of activities and corresponding text in the Procedures section for the extension stage.</p> <p>Adverse event language was updated to reflect the reporting requirements for the extension stage (including the collection of research-related injuries [RRIs]).</p> <p>Added an additional interim analysis for when Month 7 data are available from approximately the first 700 continuing subjects. The objective of the second analysis is to inform internal program-level decision making.</p>
Original protocol	01-April-2015	Not applicable (N/A)

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

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## PROTOCOL SUMMARY

### Background and Rationale

*Clostridium difficile* (*C difficile*), a gram-positive, anaerobic, spore-forming bacillus, is a major cause of antibiotic-associated nosocomial diarrhea in the developed world. In the last decade, the numbers and severity of *C difficile* iatrogenic outbreaks in hospitals and nursing homes have increased. Key factors in this escalation include emergence of hypervirulent pathogenic strains such as BI/NAP1/027, increased use of antibiotics, and increased exposure to spores in healthcare facilities.

Two large clostridial toxins, *C difficile* toxin A (TcdA) and *C difficile* toxin B (TcdB), are the principal virulence factors of *C difficile*-associated disease (CDAD) and both cause severe inflammation in the bowel. A causal relationship between toxin-producing clostridia and antibiotic-associated pseudomembranous colitis was first established in 1978. The clinical presentations of CDAD range from asymptomatic colonization to severe diarrhea, and may progress to pseudomembranous colitis, toxic megacolon, intestinal perforation, and death. Although most patients experiencing a first episode of CDAD respond well to standard antibiotic treatment, approximately 15% to 25% of the patients suffer from at least 1 recurrence. However, the risk of subsequent episodes is 33% to 65% if the patient has already experienced a first recurrence. Fecal transplantation has been shown to be rather effective in the treatment of multiple recurrences of CDAD. However, regulatory oversight of this method remains in development and, therefore, a highly effective noncumbersome treatment for complicated CDAD does not exist.

Adults above the age of 65 years are at increased risk for CDAD, particularly in the healthcare setting, and the likelihood of severe infection among adults similarly increases with age. It is anticipated that the *C difficile* vaccine will ultimately be evaluated for efficacy and safety in an older target population, whose ability to mount an immune response may be impaired: This may influence the selection of an optimal vaccination regimen to ensure short- and long-term protection.

To date, there is no vaccine available to prevent CDAD. Investigational vaccines are in clinical development, but none is licensed. Pfizer's vaccine candidate consists of a mixture of genetically modified *C difficile* toxoids A and B that are further chemically inactivated to eliminate residual cytotoxicity but retain native antigenic structure. In preclinical experiments, Pfizer's vaccine candidate was studied either alone or in combination with an adjuvant. In the hamster disease model, all vaccine formulations demonstrated a survival benefit, providing at least 90% protection from a lethal challenge with *C difficile* spores in the immunized hamsters. In nonhuman primates (NHPs), all of Pfizer's toxoid vaccine formulations tested induced robust neutralizing antitoxin antibody responses to both TcdA and TcdB.

Pfizer's *C difficile* vaccine candidate was assessed in a Phase 1 study (B5091001), conducted in the United States, where 192 healthy adults aged 50 to 85 years were enrolled. This first-in-human (FIH) study was a dose-escalating, placebo-controlled, randomized, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of *C difficile*

vaccine, as a 3-dose regimen at Months 0, 1, and 6. Three antigen dose levels (50, 100, and 200  $\mu$ g) of the vaccine candidate were assessed either alone or in combination with aluminum hydroxide.

The analysis of safety demonstrated that both formulations and all 3 dose levels were generally well tolerated. Local reactions were predominantly mild or moderate and comprised mostly injection site pain. No actual severe or Grade 4 local reactions were reported. In the 65- to 85-year age cohort, at the 200- $\mu$ g dose level, local reactions tended to occur more frequently in the toxoid-alone compared to the aluminum hydroxide-containing dose groups after all 3 doses. After all 3 doses, the frequency and severity of local reactions did not increase with increasing dose level or number of doses for any of the dose groups. Systemic events were predominantly mild to moderate and comprised mostly headache and fatigue. There was no evidence of increased frequency of systemic events with increasing dose level or number of doses for any of the dose groups.

The analysis of immunogenicity demonstrated a limited antibody response after Dose 1, but after Dose 2 there were marked increases in antibody titers against both toxin A and toxin B, which were generally maximal 7 days after Dose 2 and stable 1 month after Dose 2. Seven days after Dose 3, a substantial booster response was evident, which was slightly more marked again 1 month after Dose 3. Overall, robust antitoxin neutralizing responses were elicited by both formulations, although there was a trend for greater responses in recipients of the toxoid-alone formulation. With respect to the dose level, because of the limited sample size, 95% confidence intervals (CIs) were often overlapping for all 3 dose levels, indicating that it was not possible to discern a clear dose response.

In light of these results, a Phase 2 Study (B5091003) was designed to evaluate the safety, tolerability, and immunogenicity of the 100- and 200- $\mu$ g antigen dose levels of the toxoid-alone formulation in a 3-dose regimen administered at Days 1, 8, and 30 in healthy adults 50 to 85 years of age. Vaccinations in this study were stopped following the occurrence of 7 cases of Grade 3 injection site erythema among 162 subjects receiving the second vaccination at Day 8. Among the recipients of the active vaccine, this corresponded to an incidence of 5.0% (95% CI 2.1% to 10.1%). There were no accompanying severe systemic symptoms in the subjects, there was no report that the redness impacted their daily activities, and all local reactions fully resolved.

The local reactogenicity observed with the toxoid-alone formulation may have been due to free toxoid interacting with the elicited immune response. Since adsorption onto aluminum has been shown to bind and slowly release the vaccine constituents from the injection site, and reflecting the potential need for rapid induction of immune response and prolonged duration of protection, Study B5091009 will evaluate the safety, tolerability, and immunogenicity of 2 antigen dose levels of the aluminum hydroxide-containing vaccine (ie, 100  $\mu$ g and 200  $\mu$ g) in 2 different dosing regimens: Days 1, 8, and 30 or Months 0, 1, and 6. The primary immunogenicity endpoint will be assessed based upon a specified threshold estimate for each *C difficile* vaccine toxoid. The specified thresholds for each toxoid are considered to indicate protective titers.

Since it will be important to provide vaccinated subjects with prolonged protection against CDAD, and since individuals targeted for vaccination may have diminished capacity to mount and maintain an immune response, subjects in the present study will be followed for 4 years after their third vaccination. The purpose will be to assess antibody persistence and response to a fourth vaccination. Therefore, subjects in both dosing regimens who received the first 3 doses of *C difficile* vaccine (100 µg or 200 µg) will be enrolled into an extension stage. These subjects will receive a fourth dose of either *C difficile* vaccine at the same antigen dose level (100 µg or 200 µg) as they received previously or placebo, approximately 1 year after their third dose. These subjects will be followed for a further 3 years to assess antibody persistence. Subjects originally randomized to placebo in either dosing regimen will not continue into the extension stage.

### **Primary Endpoints and Objectives**

#### **Primary Immunogenicity Objectives**

- To describe the immunogenicity of 2 antigen dose levels (100 µg and 200 µg total toxoid) of *C difficile* vaccine when administered as a 3-dose regimen (Days 1, 8, and 30) to healthy adults aged 65 to 85 years, as measured by *C difficile* toxin A- and toxin B-specific neutralizing antibody levels at Day 37 (7 days after Dose 3).
- To describe the immunogenicity of 2 antigen dose levels (100 µg and 200 µg total toxoid) of *C difficile* vaccine when administered as a 3-dose regimen (Months 0, 1, and 6) to healthy adults aged 65 to 85 years, as measured by *C difficile* toxin A- and toxin B-specific neutralizing antibody levels at Month 7 (1 month after Dose 3).

#### **Primary Safety Objective**

- To assess the safety and tolerability of 2 antigen dose levels (100 µg and 200 µg total toxoid) of *C difficile* vaccine when administered as a 3-dose regimen (either Days 1, 8, and 30 or Months 0, 1, and 6) to healthy adults aged 65 to 85 years, by measuring local reactions and systemic events reported on subjects' electronic diaries (e-diaries), adverse events (AEs), and serious AEs (SAEs).

#### **Primary Immunogenicity Endpoints**

At Day 37 (7 days after Dose 3 for subjects receiving the Day 1, 8, and 30 regimen) and at Month 7 (1 month after Dose 3 for subjects receiving the Month 0, 1, and 6 regimen), the proportions of subjects in each vaccine group with the following:

- Toxin A-specific neutralizing antibody level (neutralization units/mL)  $\geq$  the specified threshold for toxin A;
- Toxin B-specific neutralizing antibody level (neutralization units/mL)  $\geq$  the specified threshold for toxin B; and

- Both toxin A– and toxin B–specific neutralizing antibody levels (neutralization units/mL)  $\geq$  the specified threshold for toxin A and the specified threshold for toxin B, respectively.

## Primary Safety Endpoints

- Numbers and proportions of subjects reporting local reactions (pain, erythema, and induration) and their severity, as self-reported on e-diaries for up to 14 days following Vaccinations 1, 2, and 3.
- Numbers and proportions of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain) and their severity, as self-reported on e-diaries for up to 14 days following Vaccinations 1, 2, and 3.
- Numbers and proportions of subjects reporting AEs from the first vaccination up to 28 days after the third vaccination categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).
- Numbers and proportions of subjects reporting SAEs from the first vaccination until 6 months after the third vaccination, categorized according to MedDRA.

## Study Design

This is a Phase 2, placebo-controlled, randomized, observer-blinded study to assess the safety, tolerability, and immunogenicity of 2 antigen dose levels (100  $\mu$ g and 200  $\mu$ g total toxoid) of aluminum hydroxide–containing *C difficile* vaccine administered as a 3-dose regimen: either at Days 1, 8, and 30 or Months 0, 1, and 6. Approximately 854 subjects will be enrolled in the study. Subjects will be randomly assigned in parallel in a 3:3:1 ratio to receive *C difficile* vaccine (100  $\mu$ g or 200  $\mu$ g total toxoid) or placebo (saline) in 1 of the 2 dosing regimens.

Subjects in both dosing regimens who received the first 3 doses of *C difficile* vaccine (100  $\mu$ g or 200  $\mu$ g) will be enrolled into an extension stage. These subjects will receive a fourth dose of either *C difficile* vaccine at the same antigen dose level (100  $\mu$ g or 200  $\mu$ g) as they received previously or placebo, approximately 1 year after their third dose. These subjects will be followed for a further 3 years (visits approximately every 6 months) to assess antibody persistence. Subjects originally randomized to placebo in either dosing regimen will not continue into the extension stage.

## Investigational Products

CCI

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The placebo will consist of a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose).

### **Statistical Method**

The statistical analysis of the study results will be descriptive in nature. An estimation approach will be used to assess the safety and immunogenicity objectives in the study.

## SCHEDEULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the [Study Procedures](#) and [Assessments](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

### Schedule of Activities for Subjects Assigned to Receive 3 Doses (Days 1, 8, and 30)

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 <sup>a</sup>
Visit Description	Vax 1 Day 1	Vax 2 Day 8	Day 15	Vax 3 Day 30	Day 37	Month 2	Month 4	Month 7	Month 13 (for subjects not entering the extension stage)
Visit Window (days)	1	7-11 Days After Visit 1	7-11 Days After Visit 2	20-26 Days After Visit 2	7-11 Days After Visit 4	25-35 Days After Visit 4	80-100 Days After Visit 4	165-195 Days After Visit 4	340-380 Days After Visit 4
Informed consent	X								
Demography	X								
Medical history	X								
Record nonstudy vaccinations and concomitant medications	X	X	X	X	X	X			
Physical examination, including vital signs	X								
Oral temperature	X	X		X					
Confirm eligibility	X	X	X	X	X	X	X	X	
Review temporary delay criteria	X	X		X					

**Schedule of Activities for Subjects Assigned to Receive 3 Doses (Days 1, 8, and 30)**

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 <sup>a</sup>
Visit Description	Vax 1 Day 1	Vax 2 Day 8	Day 15	Vax 3 Day 30	Day 37	Month 2	Month 4	Month 7	Month 13 (for subjects not entering the extension stage)
Visit Window (days)	1	7-11 Days After Visit 1	7-11 Days After Visit 2	20-26 Days After Visit 2	7-11 Days After Visit 4	25-35 Days After Visit 4	80-100 Days After Visit 4	165-195 Days After Visit 4	340-380 Days After Visit 4
Randomization	X								
Blood draw for immunogenicity assessment	X	X	X	X	X	X	X	X	X
Approximate total blood volume drawn per visit <sup>b</sup>	20 mL	20 mL	20 mL	20 mL	20 mL	20 mL + 40 mL <sup>c</sup>	20 mL	20 mL	20 mL
Vaccination	X	X		X					
Postvaccination observation (30 minutes) and acute AE assessment	X	X		X					
Dispense e-diary, measuring device, and thermometer	X								
Targeted physical examination, including vital signs if appropriate		X	X	X	X	X	X	X	X
Review e-diary data <sup>d</sup>	◀-----→								
Collect e-diary						X			
Record AEs	X	X	X	X	X	X	X <sup>e</sup>	X <sup>e</sup>	X <sup>e</sup>

**Schedule of Activities for Subjects Assigned to Receive 3 Doses (Days 1, 8, and 30)**

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 <sup>a</sup>
Visit Description	Vax 1 Day 1	Vax 2 Day 8	Day 15	Vax 3 Day 30	Day 37	Month 2	Month 4	Month 7	Month 13 (for subjects not entering the extension stage)
Visit Window (days)	1	7-11 Days After Visit 1	7-11 Days After Visit 2	20-26 Days After Visit 2	7-11 Days After Visit 4	25-35 Days After Visit 4	80-100 Days After Visit 4	165-195 Days After Visit 4	340-380 Days After Visit 4
Record SAEs	X	X	X	X	X	X	X	X	
Record newly diagnosed chronic medical conditions							X	X	

- a. For subjects entering the extension stage, refer to the Schedule of Activities for Subjects Participating in the Extension Stage.
- b. Minimum of 10 mL and up to 20 mL blood will be collected (prior to vaccination if at a vaccination visit).
- c. An additional blood sample of approximately 40 mL will be collected for use in development of serologic assays and reagents.
- d. E-diary data review is ongoing during subject e-diary data-entry periods (7 days after the first vaccination and 14 days after the second and third vaccinations) via an Internet-based portal.
- e. Any AEs occurring up to 48 hours after each blood draw must be recorded on the CRF.

Abbreviations: CRF = case report form; e-diary = electronic diary; Vax = vaccination.

**Schedule of Activities for Subjects Assigned to Receive 3 Doses (Months 0, 1, and 6)**

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 <sup>a</sup>
Visit Description	Vax 1 Day 1 Month 0	Vax 2 Day 30 Month 1	Day 37	Month 2	Vax 3 Month 6	Day 187	Month 7	Month 12	Month 18 (for subjects not entering the extension stage)
Visit Window (days)	1	25-35 Days After Visit 1	7-11 Days After Visit 2	25-35 Days After Visit 2	135-165 Days After Visit 2	7-11 Days After Visit 5	25-35 Days After Visit 5	165-195 Days After Visit 5	340-380 Days After Visit 5
Informed consent	X								
Demography	X								
Medical history	X								
Record nonstudy vaccinations and concomitant medications	X	X	X	X	X	X	X		
Physical examination, including vital signs	X								
Oral temperature	X	X			X				
Confirm eligibility	X	X	X	X	X	X	X	X	
Review temporary delay criteria	X	X			X				
Randomization	X								
Blood draw for immunogenicity assessment	X	X	X	X	X	X	X	X	X
Approximate total blood volume drawn per visit <sup>b</sup>	20 mL	20 mL	20 mL	20 mL + 40 mL <sup>c</sup>	20 mL	20 mL	20 mL	20 mL	20 mL
Vaccination	X	X			X				
Postvaccination observation (30 minutes) and acute AE assessment	X	X			X				
Dispense e-diary, measuring device, and thermometer	X								

**Schedule of Activities for Subjects Assigned to Receive 3 Doses (Months 0, 1, and 6)**

Visit ID	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 <sup>a</sup>
Visit Description	Vax 1 Day 1 Month 0	Vax 2 Day 30 Month 1	Day 37	Month 2	Vax 3 Month 6	Day 187	Month 7	Month 12	Month 18 (for subjects not entering the extension stage)
Visit Window (days)	1	25-35 Days After Visit 1	7-11 Days After Visit 2	25-35 Days After Visit 2	135-165 Days After Visit 2	7-11 Days After Visit 5	25-35 Days After Visit 5	165-195 Days After Visit 5	340-380 Days After Visit 5
Targeted physical examination, including vital signs if appropriate		X	X	X	X	X	X	X	X
Review e-diary data <sup>d</sup>	◀-----►								
Collect e-diary							X		
Record AEs	X	X	X	X	X	X	X	X <sup>e</sup>	X <sup>e</sup>
Record SAEs	X	X	X	X	X	X	X	X	
Record newly diagnosed chronic medical conditions								X	

- a. For subjects entering the extension stage, refer to the Schedule of Activities for Subjects Participating in the Extension Stage.
- b. Minimum of 10 mL and up to 20 mL blood will be collected (prior to vaccination if at a vaccination visit).
- c. An additional blood sample of approximately 40 mL will be collected for use in development of serologic assays and reagents.
- d. E-diary data review is ongoing during subject e-diary data-entry periods (14 days after each vaccination) via an Internet-based portal.
- e. Any AEs occurring up to 48 hours after each blood draw must be recorded on the CRF.

Abbreviations: CRF = case report form; e-diary = electronic diary; Vax = vaccination.

**Schedule of Activities for Subjects Participating in the Extension Stage**

Visit ID	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17
Visit Description	Vax 4	Day 8 After Vax 4	Day 30 After Vax 4	Month 6 After Vax 4	Month 12 After Vax 4	Month 18 After Vax 4	Month 24 After Vax 4	Month 30 After Vax 4	Month 36 After Vax 4
Visit Window (days)	340-380 Days After Vax 3 <sup>a</sup>	7-11 Days After Visit 9	25-35 Days After Visit 9	±30 Days	±30 Days	±30 Days	±30 Days	±30 Days	±30 Days
Informed consent	X								
Record nonstudy vaccinations and concomitant medications	X	X	X						
Targeted physical examination, including vital signs if appropriate	X	X	X						
Oral temperature	X								
Confirm eligibility	X	X	X	X	X	X	X	X	
Informed consent for optional blood draw <sup>b</sup>				X					
Review temporary delay criteria	X								
Rerandomization	X								
Blood draw for immunogenicity assessment	X	X	X	X	X	X	X	X	X
Approximate total blood volume drawn per visit <sup>c</sup>	20 mL	20 mL	20 mL	20 mL (up to 70 mL <sup>d</sup> )	20 mL				
Vaccination	X								
Postvaccination observation (30 minutes) and acute AE assessment	X								
Dispense e-diary, measuring device, and thermometer	X								
Review e-diary data <sup>e</sup>	◀-----→								
Collect e-diary			X						

**Schedule of Activities for Subjects Participating in the Extension Stage**

Visit ID	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17
Visit Description	Vax 4	Day 8 After Vax 4	Day 30 After Vax 4	Month 6 After Vax 4	Month 12 After Vax 4	Month 18 After Vax 4	Month 24 After Vax 4	Month 30 After Vax 4	Month 36 After Vax 4
Visit Window (days)	340-380 Days After Vax 3 <sup>a</sup>	7-11 Days After Visit 9	25-35 Days After Visit 9	±30 Days	±30 Days	±30 Days	±30 Days	±30 Days	±30 Days
Record AEs	X	X	X	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>
Record SAEs	X	X	X	X					
Record RRIs				X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>

- a. Visit 4 for subjects on the Day 1, 8, and 30 regimen and Visit 5 for subjects on the Month 0, 1, and 6 regimen.
- b. Applicable only at designated sites.
- c. Minimum of 10 mL and up to 20 mL blood will be collected (prior to vaccination if at the vaccination visit).
- d. Applicable only for subjects at designated sites who have given consent for this additional blood draw.
- e. E-diary data review is ongoing during subject e-diary data-entry periods (14 days after vaccination) via an Internet-based portal.
- f. Any AEs occurring up to 48 hours after the blood draw must be recorded on the CRF.
- g. Any RRIs occurring up to 48 hours after the blood draw must be recorded on the CRF.

Abbreviations: CRF = case report form; e-diary = electronic diary; RRI = research-related injury; Vax = vaccination.

## 1. INTRODUCTION

### 1.1. Mechanism of Action/Indication

Pfizer's *Clostridium difficile* (*C difficile*) vaccine is intended to prevent *C difficile*–associated disease (CDAD) in an at-risk population.

### 1.2. Background and Rationale

#### 1.2.1. *Clostridium difficile* Disease Background

*C difficile*, a gram-positive, anaerobic, spore-forming bacillus, is a major cause of antibiotic-associated nosocomial diarrhea in the developed world.<sup>1,2,3,4</sup> In the last decade, the numbers and severity of *C difficile* iatrogenic outbreaks in hospitals and nursing homes have increased.<sup>5</sup> Key factors in this escalation include emergence of hypervirulent pathogenic strains such as BI/NAP1/027,<sup>6,7,8</sup> increased use of antibiotics,<sup>9</sup> and increased exposure to spores in healthcare facilities.<sup>10</sup>

Two large clostridial toxins, *C difficile* toxin A (TcdA) and *C difficile* toxin B (TcdB), are the principal virulence factors of CDAD and both cause severe inflammation in the bowel.<sup>11</sup> A causal relationship between toxin-producing clostridia and antibiotic-associated pseudomembranous colitis was first established in 1978.<sup>12</sup> The clinical presentations of CDAD range from asymptomatic colonization to severe diarrhea, and may progress to pseudomembranous colitis, toxic megacolon, intestinal perforation, and death.<sup>2,13</sup> Although most patients experiencing a first episode of CDAD respond well to standard antibiotic treatment, approximately 15% to 25% of the patients suffer from at least 1 recurrence. However, the risk of subsequent episodes is 33% to 65% if the patient has already experienced a first recurrence.<sup>14,15</sup> Fecal transplantation has been shown to be rather effective in the treatment of multiple recurrences of CDAD.<sup>16,17</sup> However, regulatory oversight of this method remains in development<sup>18</sup> and, therefore, a highly effective noncumbersome treatment for complicated CDAD does not exist.

#### 1.2.2. *Clostridium difficile* Vaccine Development Rationale

Humoral immune responses to *C difficile* toxins play a significant role in preventing a more severe outcome or a recurrence of the disease in humans. Several clinical studies suggest a correlation between high serum concentrations (as measured by enzyme-linked immunosorbent assay [ELISA]) of antitoxin A immunoglobulin G (IgG) and protection from CDAD.<sup>19,20,21</sup> Active immunization with inactivated toxins and passive immunization with antitoxin antibodies have been demonstrated to protect animals from lethal challenge.<sup>22,23,24</sup> In addition, hamsters treated with vancomycin alone have a higher mortality rate compared to those treated with vancomycin plus antibody, indicating that vaccination may provide an advantage over antibiotics.<sup>22</sup> Furthermore, proof of concept that antibodies to both toxins are effective in prevention of CDAD comes from a Phase 2 study, where a combination of 2 monoclonal antibodies (mAbs) against toxin A and toxin B was tested in subjects who had already had 1 episode of CDAD.<sup>25</sup> All subjects (N=101) who received the mAbs and were protected from recurrence had approximately 10 to 100 µg of mAbs/mL in their sera. The 7 subjects who had a recurrence also exhibited similar antibody levels; however, it is not known whether the failure in protection of these 7 subjects was due to exposure to

*C difficile*-produced toxin variants not recognized by the mAbs used in the study. In the placebo group, all but 1 of the 25 subjects who suffered recurrences had less than 1 µg/mL of neutralizing antibodies in their sera.<sup>25</sup> Taken together, the Phase 2 study efficacy data suggested that antitoxin A and antitoxin B neutralizing mAb levels above a threshold of 10 µg/mL were associated with protection against CDAD. However, the minimum level of antibody required for protection could not be discerned.<sup>25</sup> Together, these findings provide a clinical rationale for the development of an anti-*C difficile* toxin A and B vaccine to prevent primary CDAD and associated disease recurrence.

Adults above the age of 65 years are at increased risk for CDAD, particularly in the healthcare setting, and the likelihood of severe infection among adults similarly increases with age.<sup>14,26,27,28,29,30</sup> It is anticipated that the *C difficile* vaccine will ultimately be evaluated for efficacy and safety in an older target population, whose ability to mount an immune response may be impaired: This may influence the selection of an optimal vaccination regimen to ensure short- and long-term protection.

To date, there is no vaccine available to prevent CDAD. Investigational vaccines are in clinical development, but none is licensed. A vaccine consisting of formalin-inactivated TcdA and TcdB is currently in Phase 3 clinical development.<sup>31,32</sup> Also, a Phase 2 study with a recombinant protein vaccine candidate incorporating truncated portions of TcdA and TcdB has recently started.<sup>33</sup>

### **1.2.3. *Clostridium difficile* Vaccine Candidate**

Pfizer's vaccine candidate consists of a mixture of genetically modified *C difficile* toxoids A and B that are further chemically inactivated to eliminate residual cytotoxicity but retain native antigenic structure.<sup>34</sup> In preclinical experiments, Pfizer's vaccine candidate was studied either alone or in combination with an adjuvant. In the hamster disease model, all vaccine formulations demonstrated a survival benefit, providing at least 90% protection from a lethal challenge with *C difficile* spores in the immunized hamsters. In nonhuman primates (NHPs), all of Pfizer's toxoid vaccine formulations tested induced robust neutralizing antitoxin antibody responses to both TcdA and TcdB.

Pfizer's *C difficile* vaccine candidate was assessed in a Phase 1 study (B5091001), conducted in the United States, where 192 healthy adults aged 50 to 85 years were enrolled. This first-in-human (FIH) study was a dose-escalating, placebo-controlled, randomized, observer-blinded trial to evaluate the safety, tolerability, and immunogenicity of *C difficile* vaccine, as a 3-dose regimen at Months 0, 1, and 6. Three antigen dose levels (50, 100, and 200 µg) of the vaccine candidate were assessed either alone or in combination with aluminum hydroxide.

The analysis of safety demonstrated that both formulations and all 3 dose levels were generally well tolerated. Local reactions were predominantly mild or moderate and comprised mostly injection site pain. No actual severe or Grade 4 local reactions were reported. In the 65- to 85-year age cohort, at the 200-µg dose level, local reactions tended to occur more frequently in the toxoid-alone compared to the aluminum hydroxide-containing dose groups (41.7%, 50.0%, and 80.0% versus 16.7%, 18.2%, and 11.1%, for any local

reaction after each of the 3 doses, respectively). After all 3 doses, the frequency and severity of local reactions did not increase with increasing dose level or number of doses for any of the dose groups. Systemic events were predominantly mild to moderate and comprised mostly headache and fatigue. There was no evidence of increased frequency of systemic events with increasing dose level or number of doses for any of the dose groups.

The analysis of immunogenicity demonstrated a limited antibody response after Dose 1, but after Dose 2 there were marked increases in antibody titers against both toxin A and toxin B, which were generally maximal 7 days after Dose 2 and stable 1 month after Dose 2. Seven days after Dose 3, a substantial booster response was evident, which was slightly more marked again 1 month after Dose 3. Overall, robust antitoxin neutralizing responses were elicited by both formulations, although there was a trend for greater responses in recipients of the toxoid-alone formulation. For example, 1 month after Dose 3 in the 65- to 85-year age cohort, the geometric mean fold rises (GMFRs) from baseline (before Dose 1) in toxin A-specific neutralizing antibody titers ranged from 131.41 to 254.77 in the toxoid-alone dose groups and from 42.73 to 80.66 in the aluminum hydroxide-containing dose groups. The corresponding ranges for toxin B-specific neutralizing antibody titers were from 2953.12 to 4922.80 and from 136.12 to 484.14, respectively. With respect to the dose level, because of the limited sample size, 95% confidence intervals (CIs) were often overlapping for all 3 dose levels, indicating that it was not possible to discern a clear dose response. Preclinical data generated by Pfizer in rhesus macaques support the use of a 3-dose regimen of *C difficile* vaccine, administered with or without aluminum hydroxide at Weeks 0, 2, and 4. Furthermore, in a rabbit toxicology study, a 4-dose regimen of *C difficile* vaccine (up to 400- $\mu$ g dose levels) given on Days 1, 8, 22, and 36 did not demonstrate adverse toxicological findings, and resulted in an increase in antitoxin A- and antitoxin B-neutralizing antibody titers, confirming the anticipated immunologic response by the animals to the administered immunogen.<sup>35</sup>

These preclinical and toxicology data, as well as the encouraging immune response observed after 3 doses in the B5091001 Phase 1 study, supported the Phase 2 Study CCI [REDACTED]

[REDACTED]

CCI [REDACTED]

[REDACTED]

CCI

[REDACTED]. These specified thresholds were derived from a Phase 2 efficacy study demonstrating that passive administration of 2 mAbs against toxin A and toxin B were associated with protection against CDAD. In addition to showing efficacy of antitoxin mAbs against recurrent CDAD, the Phase 2 efficacy study also suggested that antitoxin A- and antitoxin B-neutralizing mAb levels above a threshold of 10 µg/mL were associated with protection against CDAD recurrence.<sup>25</sup> Although the minimum level of antibody required for protection could not be discerned, the data derived from this study did allow estimation of the 50% neutralization titer elicited by the Pfizer vaccine candidate that would predict similar vaccine efficacy against CDAD CCI [REDACTED]

[REDACTED] (2) the inhibitory mAb concentration that neutralizes 50% of the toxins (IC<sub>50</sub>) had been published.<sup>22</sup>

Since it will be important to provide vaccinated subjects with prolonged protection against CDAD, and since individuals targeted for vaccination may have diminished capacity to mount and maintain an immune response, subjects in the present study will be followed for 4 years after their third vaccination. The purpose will be to assess antibody persistence and response to a fourth vaccination. Therefore, subjects in both dosing regimens who received the first 3 doses of *C difficile* vaccine (100 µg or 200 µg) will be enrolled into an extension stage and will be rerandomized in a 1:1 ratio to receive *C difficile* vaccine or placebo. These subjects will receive a fourth dose of either *C difficile* vaccine at the same antigen dose level (100 µg or 200 µg) as they received previously or placebo, approximately 1 year after their third dose. These subjects will be followed for a further 3 years to assess antibody persistence. Subjects originally randomized to placebo in either dosing regimen will not continue into the extension stage.

Complete information for this vaccine may be found in the single reference safety document (SRSD), which for this study is the investigator's brochure (IB).

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Objectives

#### 2.1.1. Primary Immunogenicity Objectives

- To describe the immunogenicity of 2 antigen dose levels (100 µg and 200 µg total toxoid) of *C difficile* vaccine when administered as a 3-dose regimen (Days 1, 8, and 30) to healthy adults aged 65 to 85 years, as measured by *C difficile* toxin A- and toxin B-specific neutralizing antibody levels at Day 37 (7 days after Dose 3).
- To describe the immunogenicity of 2 antigen dose levels (100 µg and 200 µg total toxoid) of *C difficile* vaccine when administered as a 3-dose regimen (Months 0, 1, and 6)

to healthy adults aged 65 to 85 years, as measured by *C difficile* toxin A- and toxin B-specific neutralizing antibody levels at Month 7 (1 month after Dose 3).

#### **2.1.2. Primary Safety Objective**

- To assess the safety and tolerability of 2 antigen dose levels (100 µg and 200 µg total toxoid) of *C difficile* vaccine when administered as a 3-dose regimen (either Days 1, 8, and 30 or Months 0, 1, and 6) to healthy adults aged 65 to 85 years, by measuring local reactions and systemic events reported on subjects' electronic diaries (e-diaries), adverse events (AEs), and serious AEs (SAEs).

#### **2.1.3. Secondary Immunogenicity Objectives**

- To describe the immunogenicity of 2 antigen dose levels (100 µg and 200 µg total toxoid) of *C difficile* vaccine when administered in a 3-dose regimen (either Days 1, 8, and 30 or Months 0, 1, and 6) to healthy adults aged 65 to 85 years, as measured by *C difficile* toxin A- and toxin B-specific neutralizing antibody levels at multiple time points following vaccination.
- To describe the kinetics of the immune response in healthy adults aged 65 to 85 years for up to 12 months following the administration of 3 doses of *C difficile* vaccine.
- To describe the immunogenicity of a fourth dose of *C difficile* vaccine as measured by *C difficile* toxin A- and toxin B-specific neutralizing antibody levels at multiple time points following vaccination.
- To describe the kinetics of the immune response in healthy adults aged 65 to 85 years for up to 36 months following the administration of a fourth dose of *C difficile* vaccine.

#### **2.1.4. Secondary Safety Objective**

- To assess the safety and tolerability of a fourth dose of *C difficile* vaccine by measuring local reactions and systemic events reported on subjects' e-diaries, AEs, and SAEs.

#### **2.1.5. CCI**

- CCI
- [REDACTED]
- [REDACTED]
- [REDACTED]

## 2.2. Endpoints

### 2.2.1. Primary Immunogenicity Endpoints

At Day 37 (7 days after Dose 3 for subjects receiving the Day 1, 8, and 30 regimen) and at Month 7 (1 month after Dose 3 for subjects receiving the Month 0, 1, and 6 regimen), the proportions of subjects in each vaccine group with the following:

- Toxin A-specific neutralizing antibody level (neutralization units/mL)  $\geq$  the specified threshold for toxin A;
- Toxin B-specific neutralizing antibody level (neutralization units/mL)  $\geq$  the specified threshold for toxin B; and
- Both toxin A- and toxin B-specific neutralizing antibody levels (neutralization units/mL)  $\geq$  the specified threshold for toxin A and the specified threshold for toxin B, respectively.

### 2.2.2. Primary Safety Endpoints

- Numbers and proportions of subjects reporting local reactions (pain, erythema, and induration) and their severity, as self-reported on e-diaries for up to 14 days following Vaccinations 1, 2, and 3.
- Numbers and proportions of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain) and their severity, as self-reported on e-diaries for up to 14 days following Vaccinations 1, 2, and 3.
- Numbers and proportions of subjects reporting AEs from the first vaccination up to 28 days after the third vaccination categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).
- Numbers and proportions of subjects reporting SAEs from the first vaccination until 6 months after the third dose of vaccine, categorized according to MedDRA.

### 2.2.3. Secondary Immunogenicity Endpoints

At Day 37 (7 days after Dose 3 for subjects receiving the Day 1, 8, and 30 regimen) and at Month 7 (1 month after Dose 3 for subjects receiving the Month 0, 1, and 6 regimen):

- Toxin A- and toxin B-specific neutralizing antibody levels, expressed as geometric mean concentrations (GMCs) (neutralization units/mL).
- GMFRs from baseline (before Dose 1) in
  - Toxin A-specific and
  - Toxin B-specific neutralizing antibody levels (neutralization units/mL).

- Proportions of subjects in each vaccine group with  $\geq 4$ -fold,  $\geq 8$ -fold,  $\geq 16$ -fold, and  $\geq 32$ -fold rises from baseline in
  - Toxin A-specific;
  - Toxin B-specific; and
  - Both toxin A- and toxin B-specific neutralizing antibody levels (neutralization units/mL).

For subjects receiving the Day 1, 8, and 30 regimen, on Day 1 (immediately before Dose 1), Day 8 (immediately before Dose 2), Day 15 (7 days after Dose 2), Day 30 (immediately before Dose 3), and Months 2 (1 month after Dose 3), 4 (3 months after Dose 3), 7 (6 months after Dose 3), and 13 (12 months after Dose 3); and for subjects receiving the Month 0, 1, and 6 regimen, on Day 1 (immediately before Dose 1), Day 30 (immediately before Dose 2), Day 37 (7 days after Dose 2), Months 2 (1 month after Dose 2) and 6 (immediately before Dose 3), Day 187 (7 days after Dose 3), and Months 12 (6 months after Dose 3) and 18 (12 months after Dose 3):

- Proportions of subjects in each vaccine group with
  - Toxin A-specific neutralizing antibody level (neutralization units/mL)  $\geq$  the specified threshold for toxin A;
  - Toxin B-specific neutralizing antibody level (neutralization units/mL)  $\geq$  the specified threshold for toxin B; and
  - Both toxin A- and toxin B-specific neutralizing antibody levels (neutralization units/mL)  $\geq$  the specified threshold for toxin A and the specified threshold for toxin B, respectively (these parameters will also be assessed at baseline).
- Toxin A- and toxin B-specific neutralizing antibody levels, expressed as GMCs (neutralization units/mL).
- GMFRs from baseline in
  - Toxin A-specific; and
  - Toxin B-specific neutralizing antibody levels (neutralization units/mL).
- Proportions of subjects in each vaccine group with  $\geq 4$ -fold,  $\geq 8$ -fold,  $\geq 16$ -fold, and  $\geq 32$ -fold rises from baseline in
  - Toxin A-specific;
  - Toxin B-specific; and

- Both toxin A– and toxin B–specific neutralizing antibody levels (neutralization units/mL).

For subjects enrolled in the extension stage; at the fourth dose (immediately before the fourth dose), at Days 8 and 30 after the fourth dose, and at Months 6, 12, 18, 24, 30, and 36 after the fourth dose:

- Proportions of subjects in each vaccine group with
  - Toxin A–specific neutralizing antibody level (neutralization units/mL)  $\geq$  the specified threshold for toxin A;
  - Toxin B–specific neutralizing antibody level (neutralization units/mL)  $\geq$  the specified threshold for toxin B; and
  - Both toxin A– and toxin B–specific neutralizing antibody levels (neutralization units/mL)  $\geq$  the specified threshold for toxin A and the specified threshold for toxin B, respectively (these parameters will also be assessed at baseline).
- Toxin A– and toxin B–specific neutralizing antibody levels, expressed as GMCs (neutralization units/mL).
- GMFRs from baseline in
  - Toxin A–specific; and
  - Toxin B–specific neutralizing antibody levels (neutralization units/mL).
- Proportions of subjects in each vaccine group with  $\geq 4$ -fold,  $\geq 8$ -fold,  $\geq 16$ -fold, and  $\geq 32$ -fold rises from baseline in
  - Toxin A–specific;
  - Toxin B–specific; and
  - Both toxin A– and toxin B–specific neutralizing antibody levels (neutralization units/mL).

#### **2.2.4. Secondary Safety Endpoints**

- Numbers and proportions of subjects reporting local reactions (pain, erythema, and induration) and their severity, as self-reported on e-diaries for up to 14 days following the fourth vaccination.
- Numbers and proportions of subjects reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, new or worsening muscle pain, and new or worsening joint

pain) and their severity, as self-reported on e-diaries for 14 days following the fourth vaccination.

- Numbers and proportions of subjects reporting AEs from the time of the fourth vaccination up to 28 days after the fourth vaccination categorized according to the Medical Dictionary for Regulatory Activities (MedDRA).
- Numbers and proportions of subjects reporting SAEs from the time of the fourth vaccination until 6 months after the fourth dose of vaccine, categorized according to MedDRA.

#### 2.2.5. CCI

- CCI

### 3. STUDY DESIGN

This is a Phase 2, placebo-controlled, randomized, observer-blinded study to assess the safety, tolerability, and immunogenicity of 2 antigen dose levels (100 µg and 200 µg total toxoid) of aluminum hydroxide-containing *C difficile* vaccine administered as a 3-dose regimen: either at Days 1, 8, and 30 or Months 0, 1, and 6.

Subjects will be assigned to 1 of the 2 dosing regimens and then randomly assigned in parallel in a 3:3:1 ratio to receive *C difficile* vaccine (100 µg or 200 µg total toxoid) or placebo (saline) (see [Table 1](#)).

Subjects in both dosing regimens who received the first 3 doses of *C difficile* vaccine (100 µg or 200 µg) will be enrolled into an extension stage. These subjects will receive a fourth dose of either *C difficile* vaccine at the same antigen dose level (100 µg or 200 µg) as they received previously or placebo, approximately 1 year after their third dose. These subjects will be followed for a further 3 years (visits approximately every 6 months) to assess antibody persistence. Subjects originally randomized to placebo in either dosing regimen will not continue into the extension stage.

#### 3.1. Approximate Number of Subjects

Approximately 854 healthy adults, aged 65 to 85 years will be enrolled at approximately 15 sites in the United States. The number of subjects enrolled at each site may vary based on enrollment capabilities of each site.

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

#### 3.2. Approximate Duration of Subject Participation

For the original portion of the study, subjects will be followed for 12 months after receipt of their third vaccination. Therefore, subjects assigned to the Day 1, 8, and 30 regimen will

participate for approximately 13 months and those assigned to the Month 0, 1, and 6 regimen will participate for approximately 18 months.

Subjects who enter the extension stage will be followed for a further 36 months. Therefore, subjects originally assigned to the Day 1, 8, and 30 regimen may participate for approximately 4 years and those assigned to the Month 0, 1, and 6 regimen will participate for approximately 4.5 years.

### 3.3. Approximate Duration of the Study

The original portion of the study will be completed in approximately 21 months. The total duration of the study (including the extension stage) will be approximately 5 years.

The end of the study is the last visit of the last subject as described in [Section 13](#).

### 3.4. Vaccine Groups and Enrollment

For the original portion of the study, subjects will be assigned to 1 of 6 study groups listed in Table 1. For each dosing regimen, approximately 366 subjects will receive the *C difficile* vaccine (at either 100 or 200 µg total toxoid dose level) and approximately 61 subjects will receive placebo (saline).

**Table 1. Vaccine Groups and Number of Subjects per Group and per Dose Regimen**

Vaccine Group	Vaccine Formulation Description	Dosing Regimen	Number of Subjects
1 <sup>a</sup>	Aluminum hydroxide-containing <i>C difficile</i> vaccine (100-µg antigen dose)	Days 1,8,30	183
2 <sup>a</sup>	Aluminum hydroxide-containing <i>C difficile</i> vaccine (200-µg antigen dose)	Days 1,8,30	183
3	Placebo (saline)	Days 1,8,30	61
4 <sup>a</sup>	Aluminum hydroxide-containing <i>C difficile</i> vaccine (100-µg antigen dose)	Months 0,1,6	183
5 <sup>a</sup>	Aluminum hydroxide-containing <i>C difficile</i> vaccine (200-µg antigen dose)	Months 0,1,6	183
6	Placebo (saline)	Months 0,1,6	61
<b>Total</b>			<b>854</b>

a. Subjects in these groups will be asked to enter the extension stage.

All eligible subjects who received 3 doses of *C difficile* vaccine (Groups 1, 2, 4, and 5) will be asked to enter the extension stage. Subjects enrolled in the extension stage will be rerandomized to receive a fourth dose of either *C difficile* vaccine at the same antigen dose level (100 µg or 200 µg) as they received previously or placebo.

## **4. SUBJECT SELECTION**

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

### **4.1. Inclusion Criteria**

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject has been informed of all pertinent aspects of the study.
2. Healthy male and female adults aged 65 to 85 years at enrollment (signing of the ICD) as determined by medical history, physical examination, and the clinical judgment of the investigator to be eligible for the study. Subjects with preexisting chronic medical conditions determined to be stable may be included.
3. Male subjects able to father children must agree to use a highly effective method of contraception from the time of informed consent through at least 28 days after the last dose of investigational product.
4. Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):
  - Have undergone hysterectomy and/or bilateral oophorectomy;
  - Have medically confirmed ovarian failure; or
  - Achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level confirming the post menopausal state.
5. Availability for the entire duration of the study, and able to comply with scheduled visits, treatment plan, and study procedures, including completion of the e-diary.
6. Ability to be contacted by telephone during study participation.

### **4.2. Exclusion Criteria**

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Previous administration of an investigational *C difficile* vaccine or *C difficile* mAb therapy.
2. Proven or suspected prior episode of CDAD. Please refer to the study reference manual (SRM) for additional guidance.
3. Unstable chronic medical condition or disease requiring significant change in therapy or hospitalization for worsening disease within 8 weeks before receipt of investigational product.
4. Serious chronic medical disorders, including metastatic malignancy, severe chronic obstructive pulmonary disease (COPD) requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that in the investigator's opinion precludes the subject from participating in the study.
5. Bleeding diathesis or condition associated with prolonged bleeding time that may contraindicate intramuscular injection, including subjects taking anticoagulant, antiplatelet, and/or antithrombotic agents except for low-dose daily aspirin ( $\leq 325$  mg/day) within 30 days before enrollment until 1 month after the last vaccination.
6. Any contraindication to vaccination or vaccine components, including previous anaphylactic reaction to any vaccine or vaccine-related components.
7. Subjects with congenital or acquired immunodeficiency disorders, or subjects with rheumatologic disorders or other illnesses requiring chronic treatment with known immunosuppressant medications, including mAbs, within a year of enrollment or the use of systemic corticosteroids for  $\geq 7$  days within 90 days prior to enrollment through conclusion of the study (eg,  $\geq 10$  mg/day of prednisone for  $\geq 7$  days).
8. Active or treated leukemia or lymphoma or underlying bone marrow disorder such as myelodysplasia, myeloma, or myeloproliferative disorder, treated within the past year, or any history of bone marrow transplant.
9. Malignancy that required treatment with chemotherapy (including the use of adjunctive and hormonal therapy), immunotherapy, radiation therapy, or antineoplastic target therapies within the past 24 months.
10. Subjects who received oral or parenteral antibiotics within 1 month before enrollment. Topical antibiotics are allowed.
11. Receipt of blood products or immunoglobulins (including mAbs) within 6 months before enrollment through conclusion of the study.
12. Participation in other studies involving investigational drug(s) within 30 days prior to study entry up to and including Visit 12. Participation in purely observational studies is acceptable.

13. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.
14. Females of childbearing potential; males of child-fathering potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for at least 28 days after the last dose of investigational product.
15. Residence in a nursing home or other long-term care facility, or requirement for semiskilled nursing care or assisted living. An ambulatory subject who lives in an autonomous manner in a retirement home or village is eligible for the trial.
16. A known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and/or hepatitis C virus (HCV).
17. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

#### **4.3. Inclusion Criteria for the Extension Stage**

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the extension stage.

Subjects must meet all of the following inclusion criteria to be eligible to enter the extension stage:

1. Evidence of a personally signed and dated ICD addendum indicating that the subject has been informed of all pertinent aspects of the extension stage of the study.
2. Healthy male and female adults as determined by medical history, physical examination, and the clinical judgment of the investigator to be eligible for the study. Subjects with preexisting chronic medical conditions determined to be stable may be included.
3. Receipt of all 3 doses of *C difficile* vaccine (100- $\mu$ g or 200- $\mu$ g antigen dose level) in the original portion of the study.
4. Male subjects able to father children must agree to use a highly effective method of contraception from the time of informed consent through at least 28 days after the fourth dose.
5. Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):
  - Have undergone hysterectomy and/or bilateral oophorectomy;

- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum FSH level confirming the postmenopausal state.

6. Availability for the entire duration of the study, and able to comply with scheduled visits, treatment plan, and study procedures, including completion of the e-diary.
7. Ability to be contacted by telephone during study participation.

#### **4.4. Exclusion Criteria for the Extension Stage**

Subjects with any of the following characteristics/conditions will not be eligible to enter the extension stage:

1. Subjects originally randomized to placebo in either dosing regimen during the original portion of the study.
2. Subjects who have already completed Visit 9 prior to study unblinding.
3. Previous administration of a *C difficile* mAb therapy.
4. Proven or suspected prior episode of CDAD. Please refer to the SRM for additional guidance.
5. Unstable chronic medical condition or disease requiring significant change in therapy or hospitalization for worsening disease within 8 weeks before receipt of investigational product.
6. Serious chronic medical disorders, including metastatic malignancy, severe COPD requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that in the investigator's opinion precludes the subject from participating in the study.
7. Bleeding diathesis or condition associated with prolonged bleeding time that may contraindicate intramuscular injection, including subjects taking anticoagulant, antiplatelet, and/or antithrombotic agents except for low-dose daily aspirin ( $\leq 325$  mg/day) within 30 days before until 1 month after the fourth dose.
8. Any contraindication to vaccination or vaccine components, including previous anaphylactic reaction to any vaccine or vaccine-related components.
9. Subjects with congenital or acquired immunodeficiency disorders, or subjects with rheumatologic disorders or other illnesses requiring chronic treatment with known immunosuppressant medications, including mAbs, within a year of enrollment or the use of systemic corticosteroids for  $\geq 7$  days within 90 days prior to enrollment through conclusion of the study (eg,  $\geq 10$  mg/day of prednisone for  $\geq 7$  days).

10. Active or treated leukemia or lymphoma or underlying bone marrow disorder such as myelodysplasia, myeloma, or myeloproliferative disorder, treated within the past year, or any history of bone marrow transplant.
11. Malignancy that required treatment with chemotherapy (including the use of adjunctive and hormonal therapy), immunotherapy, radiation therapy, or antineoplastic target therapies within the past 24 months.
12. Subjects who received oral or parenteral antibiotics within 1 month before the fourth dose. Topical antibiotics are allowed.
13. Receipt of blood products or immunoglobulins (including mAbs) within 6 months before enrollment through conclusion of the study.
14. Participation in other studies involving investigational drug(s) within 30 days prior to study entry up to and including Visit 12. Participation in purely observational studies is acceptable.
15. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.
16. Females of childbearing potential; males of child-fathering potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for at least 28 days after the fourth dose.
17. Residence in a nursing home or other long-term care facility, or requirement for semiskilled nursing care or assisted living. An ambulatory subject who lives in an autonomous manner in a retirement home or village is eligible for the trial.
18. A known infection with HIV, HBV, and/or HCV.
19. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for vaccination with the fourth dose.

#### **4.5. Criteria for Temporarily Delaying Vaccine Administration**

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

1. Current febrile illness (oral temperature of  $\geq 100.4^{\circ}\text{F}$  [ $38.0^{\circ}\text{C}$ ]) or other acute illness within 48 hours prior to investigational product administration.

2. Subject has received licensed nonlive influenza vaccine within the previous 14 days or any other vaccine within the previous 28 days before investigational product administration.
3. Subject has received systemic antibiotic therapy for an acute illness within 72 hours before the study vaccination.
4. If systemic corticosteroids have been administered short term (<7 days) for treatment of an acute illness, investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 1 month. Inhaled, intra-articular/intrabursal, or topical corticosteroids are permitted.

If a subject meets any delay criteria for vaccination, all study procedures, including blood sample collection relating to that visit, should be delayed until the day of vaccination.

#### **4.6. Lifestyle Guidelines**

All male subjects who are able to father children and are sexually active must agree to use a highly effective method of contraception consistently and correctly from the signing of the ICD to 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will select an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below), and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his or her designee, at each study visit, will confirm and document consistent and correct use and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy in his partner is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted, or transdermal hormonal methods of contraception is allowed provided the subject's partner remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository).
4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation, bilateral salpingectomy, or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).
6. Female partner who meets the criteria for nonchildbearing potential, as described below:
  - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
  - Have medically confirmed ovarian failure; or
  - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause.

#### **4.7. Sponsor's Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the SRM.

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

### **5. STUDY TREATMENTS**

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

#### **5.1. Allocation to Investigational Product**

Allocation of subjects to vaccine groups (at both entry to the study and entry in the extension stage) will proceed through the use of the interactive response technology (IRT) system that is accessible 24 hours a day, 365 days a year. Specific instructions for use of the IRT system will be provided under separate cover. The study site will obtain the subject's randomization

number and container number (or equivalent) assignment from the IRT system. The randomization number and the date on which the randomization number was assigned will be recorded on the case report form (CRF). Once subject numbers, container numbers, and randomization numbers have been assigned, they cannot be reassigned.

## **5.2. Blinding of Site Personnel**

In this observer-blinded study, the study staff dispensing and administering the vaccine will be unblinded, but all other site study personnel, including the principal investigator and the subject, will be blinded during the vaccination periods of the study.

Following the third interim analysis (when Month 7 [after the first dose] data are available from all continuing subjects), site personnel will be unblinded to vaccine assignments for the first 3 doses. This will enable site personnel to identify subjects eligible to enter the extension stage. During the extension stage, site personnel (excluding the study staff dispensing and administering the vaccine) will be blinded to vaccine allocation at the fourth dose until Visit 12 (6 months after the fourth dose).

The principal investigator will assign the responsibility of unblinded dispenser and unblinded administrator to persons who will not participate in the evaluation of any study subject. More than 1 unblinded dispenser/administrator may be assigned per site. A member of the study site staff or clinic pharmacy should fulfill this role. Contact between the unblinded dispenser and study subjects should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispenser/administrator must not be allowed to know the investigational product assigned to any study subject and must not be allowed to see the investigational product container contents.

## **5.3. Blinding of the Sponsor**

Those study team members who are involved in ensuring that protocol requirements for investigational product handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study. All other study team members will remain blinded to vaccine assigned/received at Doses 1, 2, and 3 until the third interim analysis. Those study team members will also be blinded to vaccine assigned/received at Dose 4 until Visit 12 (6 months after the fourth dose). Laboratory personnel performing the immunologic assays will remain blinded to vaccine assigned/received throughout the study. Certain sponsor personnel not involved in the conduct of the study will review unblinded data as defined in an internal review committee (IRC) charter per Pfizer standard operating procedures (SOPs). In addition to the IRC members, an unblinded statistician, an unblinded physician, and an unblinded clinical scientist, who are not part of the study team, will be assigned to work with an external independent statistical center supporting the IRC and external data monitoring committee (E-DMC) review activities.

## **5.4. Breaking the Blind**

At the initiation of the study, each study site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the

investigator or subinvestigator consults with a member of the study team prior to breaking the blind. If this is not possible within the time frame required for breaking the blind, a member of the study team should be contacted as soon as possible afterwards. The breaking of the blind will be recorded in the appropriate section of the CRF.

At the appropriate time points for unblinding, site personnel will be able to access subject vaccine allocations for Doses 1, 2, and 3 and Dose 4 using the IRT system.

## **5.5. Vaccine Supplies**

### **5.5.1. Formulation and Packaging**

#### **5.5.1.1. *Clostridium difficile* Vaccine**

CCI



#### **5.5.1.2. Placebo**

The placebo will consist of a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose) and will be provided by the sponsor to each study site. The placebo will be packaged within cartons labeled by Pfizer or its designee in accordance with current guidelines and applicable local and legal regulatory requirements. Blinded, sealed cartons will contain 1 single-use 2-mL vial of placebo. Refer to the DAI for details regarding the preparation and dispensing of placebo.

#### **5.5.2. Preparation and Dispensing**

See the dosage and administration instructions (DAI) for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced **unblinded** member of the study



staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

### **5.5.3. Administration**

All injections will be administered in the upper deltoid muscle, preferably of the nondominant arm, by the **unblinded** administrator. For subjects receiving vaccinations on the Day 1, 8, and 30 regimen, prior to the second and third vaccinations, appropriate **blinded** site staff should evaluate the injection site for any ongoing reactions from the previous vaccination. If an injection site reaction is still present, investigational product should be administered by intramuscular injection in the upper deltoid muscle of the opposite arm.

Subjects on the Day 1, 8, and 30 regimen will receive 1 dose of *C difficile* vaccine/placebo at Visits 1 [Day 1], 2 [Day 8], and 4 [Day 30]). Subjects on the Month 0, 1, and 6 regimen will receive 1 dose of *C difficile* vaccine/placebo at Visits 1 [Day 1], 2 [Day 30], and 5 [Month 6]). Subjects entering the extension stage will receive 1 dose of *C difficile* vaccine/placebo at Visit 9. Administration of investigational products should be performed by an appropriately qualified, Good Clinical Practice (GCP)-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard vaccination practices.

Investigational product administration details (ie, date of administration, randomization number, volume, route, and site of administration, and administration errors) will be recorded on the CRF. Investigational product accountability will be documented as per [Section 5.7](#).

### **5.5.4. Compliance**

All doses of investigational product will be administered by the appropriately designated **unblinded** study staff at the investigative site. The information will be recorded on source documents, on the investigational product accountability record, and in the CRF.

## **5.6. Investigational Product Storage**

At each site, the investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. Storage conditions stated in the SRSD (ie, IB) will be superseded by the storage conditions stated in the label.

CCI



CCI

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Guidance on temperature monitoring and procedures for the review of temperature deviations will be provided in the investigational product manual. Preparation instructions and stability information can be found in the DAI.

## **5.7. Investigational Product Accountability**

The unblinded vaccine dispenser must maintain a complete and current accountability record, documenting the receipt, use, loss, or other disposition of the investigational product supplies.

Investigational product accountability applies to such products when they are required by the protocol and supplied (shipped) by the sponsor (including aluminum hydroxide diluent specified for reconstitution).

### **5.7.1. Destruction of Investigational Product Supplies**

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

## **5.8. Concomitant Medication(s)**

### **5.8.1. Recording Concomitant Vaccinations and Medications**

Subjects will be asked to provide a history of the name and date for all vaccinations received from 6 months prior to enrollment until 1 month after the third vaccination (Visit 6 [Month 2] for subjects on the Day 1, 8, and 30 regimen and Visit 7 [Month 7] for subjects on the Month 0, 1, and 6 regimen) and this information will be recorded in the CRF.

Subjects entering the extension stage will be asked to provide a history of the name and date for all vaccinations received from 28 days prior to vaccination with the fourth dose until Visit 11 (Day 30 after the fourth dose), and this information will be recorded in the CRF.

Subjects will be asked to provide the start date, stop date, dose, unit, frequency, route, and indication for concomitant medications taken after signing the ICD until 1 month after the third vaccination (Visit 6 [Month 2] for subjects on the Day 1, 8, and 30 regimen and Visit 7 [Month 7] for subjects on the Month 0, 1, and 6 regimen). Details of this information will be recorded in the CRF.

Subjects will be asked to provide the start date, stop date, dose, unit, frequency, route, and indication for concomitant medications taken from the time of vaccination with the fourth dose until Visit 11 (Day 30 after the fourth dose), and this information will be recorded in the CRF.

### **5.8.2. Prohibited Concomitant Vaccinations, Medications, and Blood Products**

Unless considered medically necessary, no vaccines (licensed or investigational) other than study vaccine should be administered between signing the ICD and 1 month after the third vaccination (Visit 6 [Month 2] for subjects on the Day 1, 8, and 30 regimen and Visit 7 [Month 7] for subjects on the Month 0, 1, and 6 regimen) or from the time of the fourth dose until Visit 11 (Day 30 after the fourth dose). Whenever possible, any nonstudy vaccine that is considered medically necessary should be administered at least 28 days after, or at least 28 days prior to, administration of study vaccine. Note one exception: licensed nonlive influenza vaccine may be administered at least 14 days after, or at least 14 days prior to, the administration of study vaccine.

Immunosuppressive therapy is prohibited throughout the study; this includes chemotherapy agents or immune-modifying drugs, the latter including, but not limited to, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and the tumor necrosis factor antagonists, and immune response modifiers such as, but not limited to, ustekinumab. Use of systemic corticosteroids ( $\geq 10$  mg/day of prednisone or equivalent) for  $\geq 7$  days is prohibited within 90 days prior to enrollment through the conclusion of the study.

Any blood products, including immunoglobulin, are also prohibited throughout the course of the study.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with investigational product administration are not permitted. However, if a subject is taking a

permitted medication (according to Section 5.8.3) for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

An e-diary will be used to capture the use of antipyretics/pain medication to treat local reactions and systemic events for 7 or 14 days (dependent upon assigned vaccination regimen) following the first vaccination and 14 days following the second and third vaccinations as described in [Section 7.1.1](#). For subjects entering the extension stage, the e-diary will capture the use of antipyretics/pain medication to treat local reactions and systemic events for 14 days after the fourth dose as described in [Section 7.1.1](#).

### **5.8.3. Permitted Concomitant Medications**

The use of antipyretics and other pain medication to treat symptoms associated with investigational product administration or ongoing conditions is permitted.

Medication other than that described as prohibited in [Section 5.8.2](#) required for treatment of preexisting stable conditions is permitted.

Inhaled, topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

Low-dose aspirin ( $\leq 325$  mg/day) is permitted when used as an antiplatelet agent.

## **6. STUDY PROCEDURES**

The schedule of procedures is presented in the [Schedule of Activities](#). In order for the study visits to be scheduled within the correct time frames, the day of the first vaccination should be considered Day 1.

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

Before randomization, the investigator or a medically qualified designee will review the subject's medical history and medications to ensure that the subject meets all of the inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria. The procedures required at each visit are detailed below.

### **6.1. Day 1, 8, and 30 Regimen**

#### **6.1.1. Visit 1: Day 1 - Vaccination 1**

- Obtain written informed consent prior to performing any protocol-required procedures.
- Record the subject's demography (including date of birth, sex, race, and ethnicity).

- Record medical history of significance, including the presence of chronic medical conditions and relevant surgical procedures.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Perform a physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, abdomen, extremities, neurological, and lymph nodes. Abnormal results must be recorded on source documents and the medical history CRF.
- Perform vital sign measurements, including weight, height, sitting blood pressure, sitting pulse rate, and respiratory rate. When multiple measurements are taken for the same time point, the most out-of-range (eg, highest or lowest) value must be reported. (See the SRM for additional guidance.)
- Measure and record the subject's oral temperature.
- Ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met ([Section 4](#)).
- An appropriate site staff member (may be blinded or unblinded) will use the IRT system to obtain the subject's randomization number and investigational product blinded carton number. Unblinded site staff will prepare and administer investigational product. Please refer to the SRM under separate cover for further instruction on this process.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Investigational product will be administered by intramuscular injection, by the unblinded administrator, into the upper deltoid muscle, preferably of the nondominant arm.
- The unblinded vaccine administrator updates the investigational product accountability records.
- Blinded study staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded as immediate AEs.
- Record and report AEs and SAEs (relative to the time of vaccination) as described in [Section 8](#) and the [Schedule of Activities](#).
- Issue a measuring device for measurement of local reactions, and a digital thermometer for recording of daily temperatures, and provide instructions on their use.
- Issue a subject e-diary and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.
  - Any severe systemic event within 7 days following vaccination.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

#### **6.1.2. Visit 2: Day 8 - Vaccination 2 (7 to 11 Days After Visit 1)**

- Review the subject's e-diary data and follow up on any ongoing local reactions or systemic events.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.

- Measure and record the subject's oral temperature.
- Ensure that none of the temporary delay criteria are met ([Section 4.5](#)).
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- An appropriately qualified **blinded** member of the site staff should evaluate the previous injection site for any ongoing reactions from the previous vaccination. If there is no persisting injection site reaction from the previous vaccine administration, the investigational product should be administered by the **unblinded** administrator. If an injection site reaction is still present, investigational product should be administered by intramuscular injection in the upper deltoid muscle of the opposite arm by the **unblinded** administrator.
- The unblinded vaccine administrator updates the investigational product accountability records.
- Blinded study staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded as immediate AEs.
- Record and report AEs and SAEs (relative to the time of vaccination) as described in [Section 8](#) and the [Schedule of Activities](#).
- Remind the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination. Instruct the subject that e-diary entries for injection site symptoms should be in relation to the vaccination received that day and not to the previous vaccination.
- Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.
  - Any severe systemic event within 7 days following vaccination.
  - If any new, late-onset reaction occurs from the previous vaccination.
  - If any ongoing reaction from the previous vaccination worsens.

- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

#### **6.1.3. Visit 3: Day 15 (7 to 11 Days After Visit 2)**

- Review the subject's e-diary data and remind the subject to continue completing the e-diary up to Day 14.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.

- Any severe systemic event within 14 days following vaccination.
- If any new, late-onset reaction occurs from the previous vaccination.
- If any ongoing reaction from the previous vaccination worsens.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

#### **6.1.4. Visit 4: Day 30 - Vaccination 3 (20 to 26 Days After Visit 2)**

- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Review the subject's e-diary data from Dose 2 and follow up on any ongoing local reactions or systemic events.
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Measure and record the subject's oral temperature.
- Ensure that none of the temporary delay criteria are met ([Section 4.5](#)).
- Collect a blood sample of approximately 20 mL for immunogenicity assessments ([Section 7.2](#)).

- An appropriately qualified **blinded** member of the site staff should evaluate the previous injection site for any ongoing reactions from the previous vaccination. If there is no persisting injection site reaction from the previous vaccine administration, the investigational product should be administered by the **unblinded** administrator. If an injection site reaction is still present, investigational product should be administered by intramuscular injection in the upper deltoid muscle of the opposite arm by the **unblinded** administrator.
- The unblinded vaccine administrator updates the investigational product accountability records.
- Blinded study staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded as immediate AEs.
- Record and report AEs and SAEs (relative to the time of vaccination) as described in [Section 8](#) and the [Schedule of Activities](#).
- Remind the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination. Instruct the subject that e-diary entries for injection site symptoms should be in relation to the vaccination received that day and not to the previous vaccination.
- Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.
  - Any severe systemic event within 14 days following vaccination.
  - If any new, late-onset reaction occurs from the previous vaccination.
  - If any ongoing reaction from the previous vaccination worsens.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.

- Complete the CRF.

#### **6.1.5. Visit 5: Day 37 (7 to 11 Days After Visit 4)**

- Review the subject's e-diary data and remind the subject to continue completing the e-diary up to Day 14.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.
  - Any severe systemic event within 14 days following vaccination.
  - If any new, late-onset reaction occurs from the previous vaccination.
  - If any ongoing reaction from the previous vaccination worsens.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

#### **6.1.6. Visit 6: Month 2 (25 to 35 Days After Visit 4)**

- Review the subject's e-diary data after Dose 3 and follow up on any ongoing local reactions or systemic events.
- Collect the subject's e-diary.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)). An additional blood sample of approximately 40 mL will be obtained.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.1.7. Visit 7: Month 4 (80 to 100 Days After Visit 4)**

- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).

- Based on clinical evaluation, determine whether any newly diagnosed chronic medical conditions or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing. In addition, any AEs occurring up to 48 hours after the blood draw will be recorded.
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.1.8. Visit 8: Month 7 (165 to 195 Days After Visit 4)**

- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any newly diagnosed chronic medical conditions or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing. In addition, any AEs occurring up to 48 hours after the blood draw will be recorded.
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

### **6.1.9. Visit 9: Month 13 (340 to 380 Days After Visit 4)**

- If study-level unblinding following the third interim analysis has already occurred ([Section 5.3](#)), use the IRT system to determine if the subject received *C difficile* vaccine (not placebo) at Doses 1, 2, and 3. If the subject received *C difficile* vaccine (at either antigen dose level of 100 µg or 200 µg), obtain consent for the subject to enter the extension stage ([Section 6.3](#)).

**For subjects entering the extension stage, follow the procedures in [Section 6.3.1](#) rather than the procedures listed below. For the subjects not entering the extension stage, complete the procedures below.**

- Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing. In addition, any AEs occurring up to 48 hours after the blood draw will be recorded.
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Complete the source documents.
- Complete the CRF.

## **6.2. Month 0, 1, and 6 Regimen**

### **6.2.1. Visit 1: Day 1 - Vaccination 1**

- Obtain written informed consent prior to performing any protocol-required procedures.
- Record the subject's demography (including date of birth, sex, race, and ethnicity).
- Record medical history of significance, including the presence of chronic conditions and relevant surgical procedures.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Perform a physical examination evaluating any clinically significant abnormalities within the following body systems: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, abdomen, extremities, neurological, and lymph nodes. Abnormal results must be recorded on source documents and the medical history CRF.

- Perform vital sign measurements, including weight, height, sitting blood pressure, sitting pulse rate, and respiratory rate. When multiple measurements are taken for the same time point, the most out-of-range (eg, highest or lowest) value must be reported. (See the SRM for guidance.)
- Measure and record the subject's oral temperature.
- Ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met ([Section 4](#)).
- An appropriate site staff member (may be blinded or unblinded) will use the IRT system to obtain the subject's randomization number and investigational product blinded carton number. Unblinded site staff will prepare and administer investigational product. Please refer to the SRM under separate cover for further instruction on this process.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Investigational product will be administered by intramuscular injection, by the unblinded administrator, into the upper deltoid muscle, preferably of the nondominant arm.
- The unblinded vaccine administrator updates the investigational product accountability records.
- Blinded study staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded as immediate AEs.
- Record and report AEs and SAEs (relative to the time of vaccination) as described in [Section 8](#) and the [Schedule of Activities](#).
- Issue a measuring device for measurement of local reactions, and a digital thermometer for recording of daily temperatures, and provide instructions on their use.
- Issue a subject e-diary and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination.
- Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.

- Any severe systemic event within 14 days following vaccination.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

#### **6.2.2. Visit 2: Day 30 - Vaccination 2 (25 to 35 Days After Visit 1)**

- Review the subject's e-diary data and follow up on any ongoing local reactions or systemic events.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Measure and record the subject's oral temperature.
- Ensure that none of the temporary delay criteria are met ([Section 4.5](#)).
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Investigational product will be administered by intramuscular injection, by the unblinded administrator, into the upper deltoid muscle, preferably of the nondominant arm.
- The unblinded vaccine administrator updates the investigational product accountability records.

- Blinded study staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded as immediate AEs.
- Record and report AEs and SAEs (relative to the time of vaccination) as described in [Section 8](#) and the [Schedule of Activities](#).
- Remind the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination. Instruct the subject that e-diary entries for injection site symptoms should be in relation to the vaccination received that day and not to the previous vaccination.
- Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.
  - Any severe systemic event within 7 days following vaccination.
  - If any new, late-onset reaction occurs from the previous vaccination.
  - If any ongoing reaction from the previous vaccination worsens.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.2.3. Visit 3: Day 37 (7 to 11 Days After Visit 2)**

- Review the subject's e-diary data and remind subjects to continue completing the e-diary up to Day 14.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).

- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.
  - Any severe systemic event within 14 days following vaccination to determine if an unscheduled visit is required.
  - If any new, late-onset reaction occurs from the previous vaccination.
  - If any ongoing reaction from the previous vaccination worsens.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

#### **6.2.4. Visit 4: Month 2 (25 to 35 Days After Visit 2)**

- Review the subject's e-diary data after Dose 2 and follow up on any ongoing local reactions or systemic events.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)). An additional blood sample of approximately 40 mL will be obtained.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.2.5. Visit 5: Month 6 - Vaccination 3 (135 to 165 Days After Visit 2)**

- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's

self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.

- Measure and record the subject's oral temperature.
- Ensure that none of the temporary delay criteria are met ([Section 4.5](#)).
- Collect a blood sample of approximately 20 mL for immunogenicity assessments ([Section 7.2](#)).
- Investigational product will be administered by intramuscular injection, by the unblinded administrator, into the upper deltoid muscle, preferably of the nondominant arm. The unblinded vaccine administrator updates the investigational product accountability records.
- Blinded study staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded as immediate AEs.
- Record and report AEs and SAEs (relative to the time of vaccination) as described in [Section 8](#) and the [Schedule of Activities](#).
- Remind the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination. Instruct the subject that e-diary entries for injection site symptoms should be in relation to the vaccination received that day and not to the previous vaccination.
- Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).
  - Any peeling/scaling or blackening of the skin at the injection site.
  - Severe arm pain.
  - Any severe systemic event within 7 days following vaccination.
  - If any new, late-onset reaction occurs from the previous vaccination.
  - If any ongoing reaction from the previous vaccination worsens.

- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

#### **6.2.6. Visit 6: Day 187 (7 to 11 Days After Visit 5)**

- Review the subject's e-diary data and remind subjects to continue completing the e-diary up to Day 14.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

#### **6.2.7. Visit 7: Month 7 (25 to 35 Days After Visit 5)**

- Review the subject's e-diary data after Dose 3 and follow up on any ongoing local reactions or systemic events.
- Collect the subject's e-diary.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.2.8. Visit 8: Month 12 (165 to 195 Days After Visit 5)**

- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in [Section 6.5](#).
- Based on clinical evaluation, determine whether any newly diagnosed chronic medical conditions or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing. In addition, any AEs occurring up to 48 hours after the blood draw will be recorded.
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).

- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.2.9. Visit 9: Month 18 (340 to 380 Days After Visit 5)**

- If study-level unblinding following the third interim analysis has already occurred ([Section 5.3](#)), use the IRT system to determine if the subject received *C difficile* vaccine (not placebo) at Doses 1, 2, and 3. If the subject received *C difficile* vaccine (at either antigen dose level of 100 µg or 200 µg), obtain consent for the subject to enter the extension stage ([Section 6.3](#)).

**For subjects entering the extension stage, follow the procedures in [Section 6.3.1](#) rather than the procedures listed below. For the subjects not entering the extension stage, complete the procedures below.**

- Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing. In addition, any AEs occurring up to 48 hours after the blood draw will be recorded.
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Complete the source documents.
- Complete the CRF.

### **6.3. Extension Stage**

#### **6.3.1. Visit 9: Vaccination 4 (340 to 380 Days After Vaccination 3)**

- Obtain written informed consent for participation in the extension stage prior to performing any of the extension-stage procedures.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).

- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Measure and record the subject's oral temperature.
- Ensure that all inclusion criteria for the extension stage, none of the exclusion criteria for the extension stage, and none of the temporary delay criteria are met ([Section 4](#)).
- An appropriate site staff member (may be blinded or unblinded) will use the IRT system to obtain the subject's randomization number for the extension stage and investigational product blinded carton number. Unblinded site staff will prepare and administer investigational product. Please refer to the SRM under separate cover for further instruction on this process.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Investigational product will be administered by intramuscular injection, by the unblinded administrator, into the upper deltoid muscle, preferably of the nondominant arm.
- The unblinded vaccine administrator updates the investigational product accountability records.
- Blinded study staff will observe the subject for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded as immediate AEs.
- Record and report AEs and SAEs (relative to the time of vaccination) as described in [Section 8](#) and the [Schedule of Activities](#).
- Issue a measuring device for measurement of local reactions, and a digital thermometer for recording of daily temperatures, and provide instructions on their use.
- Issue a subject e-diary and provide instructions on its completion. Ask the subject to complete the e-diary from Day 1 to Day 14, with Day 1 being the day of vaccination. Ask the subject to contact the site staff or investigator immediately, to determine if an unscheduled visit is required, if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).

- Any peeling/scaling or blackening of the skin at the injection site.
- Severe arm pain.
- Any severe systemic event within 14 days following vaccination.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

### **6.3.2. Visit 10: Day 8 After Vaccination 4 (7 to 11 Days After Visit 9)**

- Review the subject's e-diary data and remind subjects to continue completing the e-diary up to Day 14.
- Ensure that the subject continues to be eligible for the study (see [Section 6.5](#)).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Ask the subject to contact the site staff or investigator immediately if he or she experiences any of the following:
  - Fever  $\geq 39.0^{\circ}\text{C}$  ( $\geq 102.1^{\circ}\text{F}$ ).
  - Redness or swelling at the injection site measuring greater than 10 cm ( $\geq 21$  measuring device units).

- Any peeling/scaling or blackening of the skin at the injection site.
- Severe arm pain.
- Any severe systemic event within 14 days following vaccination to determine if an unscheduled visit is required.
- If any new, late-onset reaction occurs from the previous vaccination.
- If any ongoing reaction from the previous vaccination worsens.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Remind the subject to bring the completed e-diary to the next visit.
- Complete the source documents.
- Complete the CRF.

### **6.3.3. Visit 11: Day 30 After Vaccination 4 (25 to 35 Days After Visit 9)**

- Review the subject's e-diary data after Dose 4 and follow up on any ongoing local reactions or systemic events.
- Collect the subject's e-diary.
- Ensure that the subject continues to be eligible for the study (see [Section 6.5](#)).
- Based on clinical evaluation, determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines and concomitant medications as described in [Section 5.8.1](#).
- Conduct a targeted physical examination, including vital signs if appropriate, evaluating any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the last visit. Abnormal results, including those that indicate worsening of medical history conditions, must be recorded on source documents and the AE CRF (with recording of time relative to vaccination) as appropriate.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).

- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.3.4. Visit 12: Month 6 After Vaccination 4 ( $\pm 30$ Days)**

- Ensure that the subject continues to be eligible for the study (see [Section 6.5](#)).
- Based on clinical evaluation, determine whether any SAEs have occurred since the last study visit. Record and report findings as described in [Section 8](#) and the [Schedule of Activities](#). Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing. In addition, any AEs or research-related injuries (RRIs) occurring up to 48 hours after the blood draw will be recorded.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- For subjects at designated sites who have consented to the additional blood draw, collect a whole blood sample of approximately 20 to 50 mL for exploratory testing (see details below\*).
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

\*For sites to participate in collection of blood samples for exploratory purposes, the following additional procedures will be completed:

Obtain written informed consent from subjects agreeing to the additional blood draw.

Obtain additional blood sample of 20 to 50 mL for exploratory purposes. Maximum amount of blood to be obtained at this visit for those subjects participating is up to 70 mL.

#### **6.3.5. Visit 13: Month 12 After Vaccination 4 ( $\pm 30$ Days)**

- Ensure that the subject continues to be eligible for the study (see [Section 6.5](#)).
- Record any AEs or RRIs that occurred up to 48 hours after the previous blood draw as described in [Section 8](#) and the [Schedule of Activities](#). Review any AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.

- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.3.6. Visit 14: Month 18 After Vaccination 4 ( $\pm 30$ Days)**

- Ensure that the subject continues to be eligible for the study (see [Section 6.5](#)).
- Record any AEs or RRIs that occurred up to 48 hours after the previous blood draw as described in [Section 8](#) and the [Schedule of Activities](#). Review any AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.3.7. Visit 15: Month 24 After Vaccination 4 ( $\pm 30$ Days)**

- Ensure that the subject continues to be eligible for the study (see [Section 6.5](#)).
- Record any AEs or RRIs that occurred up to 48 hours after the previous blood draw as described in [Section 8](#) and the [Schedule of Activities](#). Review any AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.3.8. Visit 16: Month 30 After Vaccination 4 ( $\pm 30$ Days)**

- Ensure that the subject continues to be eligible for the study (see [Section 6.5](#)).
- Record any AEs or RRIs that occurred up to 48 hours after the previous blood draw as described in [Section 8](#) and the [Schedule of Activities](#). Review any AEs that were

ongoing from the previous visit and record their stop dates or confirm if they are still continuing.

- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Schedule an appointment for the subject to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

#### **6.3.9. Visit 17: Month 36 After Vaccination 4 ( $\pm 30$ Days)**

- Record any AEs or RRIs that occurred up to 48 hours after the previous blood draw as described in [Section 8](#) and the [Schedule of Activities](#). Review any AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Collect a blood sample of approximately 20 mL for immunogenicity testing ([Section 7.2](#)).
- Complete the source documents.
- Complete the CRF.

#### **6.4. Severe Reaction Assessment and Unscheduled Visits**

If a severe local reaction ([Section 7.1.1.2](#)), severe systemic event ([Section 7.1.1.3](#)), or severe fever ([Section 7.1.1.4](#)) is reported between scheduled visits, a telephone contact must occur as soon as possible between the investigator or medically qualified member of the study staff and the subject to assess if an unscheduled site visit is required. A site visit must be scheduled as soon as possible to assess the extent of the reaction, unless:

- The subject is unable to attend the unscheduled visit, or
- The reaction is no longer present at the time of the telephone contact, or
- The investigator confirms that the data were entered into the e-diary in error by the subject.

This telephone contact will be recorded in the subject source documents and the CRF.

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

Reactions should be assessed by the investigator or medically qualified member of the study staff. For the purpose of reaction assessment, a medically qualified member of the study staff is a study physician or a study nurse, as applicable to the investigator's local practice. If a

severe local reaction, severe systemic event, or severe fever is suspected at a scheduled visit, the same assessments should be conducted.

Assessment should include the following:

- Measure oral temperature (°C or °F).
- Measure minimum and maximum diameter (cm) of any redness present.
- Measure minimum and maximum diameter (cm) of any swelling present.
- Assess any pain present in accordance with the grades provided in [Section 7.1.1.3](#).
- Assess for lymphadenopathy associated with any local reaction present.
- Assess any systemic event (vomiting, diarrhea, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain) that is present.
- Determine whether any of the reported symptoms or signs meet Grade 4 and/or SAE reporting criteria (refer to [Section 7.1.1.2](#), [Section 7.1.1.3](#), [Section 7.1.1.4](#), and [Section 8.6](#)).

An extra visit may also be scheduled for assessment of any other AE.

## 6.5. Subject Withdrawal

Subject eligibility must be confirmed at each visit in order to continue in the study. Inclusion criteria [2](#), [3](#), [4](#), and [5](#) and exclusion criteria [4](#), [7](#), [8](#), [9](#), [11](#), [12](#), [13](#), [15](#), and [16](#) should be considered before a subject is withdrawn at any point during the study. Exclusion criteria [3](#), [5](#), [6](#), and [14](#) should be considered before a subject is withdrawn during the vaccination phase (refer to [Section 4](#)).

During the extension stage, inclusion criteria [1](#), [6](#), and [7](#) for the extension stage and exclusion criteria [1](#), [4](#), [15](#), and [19](#) for the extension stage should be considered before a subject is withdrawn at any point during the study. Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site. If a subject experiences a confirmed Grade 3 or 4 local reaction, a confirmed Grade 4 systemic event, or a confirmed Grade 4 fever or SAE determined to be related to the administration of the investigational product, further vaccinations will be discontinued in that subject.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. Procedures for managing lost-to-follow-up subjects are described in the SRM. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all

study-related materials (ie, e-diary), request the subject to return for a final visit, if applicable (as defined below), and follow up with the subject regarding any unresolved AEs.

When a subject discontinues or meets criteria for withdrawal, the investigator will notify the sponsor and, when possible, will perform the procedures for the next scheduled visit.

Additionally, where possible, the investigator must contact the subject by phone 12 months after his or her third vaccination and invite the subject to visit the study site to conduct the procedures detailed for Visit 9 as per [Section 6.1.9](#) (excluding subjects entering the extension stage). If the subject is unwilling or unable to come in for the visit, the investigator will record whether any newly diagnosed chronic medical conditions or SAEs have occurred since the last study visit.

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

Additional subjects will not be enrolled to replace discontinued/withdrawn subjects following receipt of the first study vaccination.

## 7. ASSESSMENTS

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

### 7.1. Safety

Safety parameters will be assessed as described in the [Schedule of Activities](#), [Section 6](#), [Section 8](#), and below.

A medical history and physical examination including measurement of vital signs will be performed on all subjects at Visit 1 to establish a baseline. At all subsequent visits during the original portion of the study, and at Visits 9, 10, and 11 during the extension stage, a targeted physical examination (including vital sign measurement if appropriate) will be performed, to evaluate any clinically significant abnormalities based on history and the participant's self-reported symptoms or complaints since the previous visit. Significant medical history and observations from the physical examination will be documented in the CRF.

The safety parameters include e-diary reports of local reactions and systemic events that occur in the 14 days (or 7 days for the first vaccination for subjects on the Day 1, 8, and 30

regimen) after investigational product administration. These prospectively collected occurrences of local reactions and systemic events are graded as described in [Section 7.1.1](#).

Acute reactions within the first 30 minutes after investigational product administration will be assessed and documented in the AE CRF.

In addition, AEs, newly diagnosed chronic medical conditions, SAEs, and RRIs are collected, recorded, and reported as defined in [Section 8](#).

### **7.1.1. Electronic Diary**

The subject will be issued an e-diary, based on a smartphone or equivalent technology, and will be asked to monitor and record local reactions, systemic events, and the use of antipyretics/pain medication to treat symptoms for 14 days following vaccination (or 7 days following the first vaccination for subjects on the Day 1, 8, and 30 regimen). The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions, systemic events, and use of antipyretics/pain medication to treat symptoms reported on the e-diary will be transferred electronically to the e-diary vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an Internet-based portal. E-diary data review is ongoing during subject e-diary data-entry periods (7 days after the first vaccination and 14 days after the second, third, and fourth [if applicable] vaccinations) via an Internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF.

Investigators (or designee) will be required to review the e-diary data online at frequent intervals as part of the ongoing safety review.

The investigator or designee must contact the subject in order to obtain stop dates for any ongoing local reactions or systemic events or continuing use of antipyretic/pain medication to treat symptoms on the last day that the e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

#### **7.1.1.1. Grading Scales**

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.<sup>37</sup>

#### **7.1.1.2. Local Reactions**

During the e-diary reporting period, subjects will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary. If a local reaction persists beyond the end of the e-diary period following vaccination, the subject will be

requested to report that information and any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21+), and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 2. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the subject as absent, mild, moderate, or severe according the grading scale in Table 2.

A subject with a severe local reaction at the injection site will be prompted to contact the investigator to assess the reaction and perform an unscheduled visit as appropriate. Only an investigator or medically qualified person is able to classify a subject's local reaction as Grade 4. If a subject experiences a suspected Grade 4 local reaction, the investigator must immediately notify the sponsor. If a subject experiences a confirmed Grade 3 or 4 local reaction determined to be related to the administration of the investigational product, further vaccinations will be discontinued in that subject.

**Table 2. Local Reaction Grading Scale**

	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Grade 4</b>
<b>Pain</b>	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization
<b>Erythema/ Redness</b>	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 ( $\geq 21$ measuring device units)	Necrosis or exfoliative dermatitis
<b>Induration/ Swelling</b>	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 ( $\geq 21$ measuring device units)	Necrosis

#### 7.1.1.3. Systemic Events

During the e-diary reporting period, subjects will be asked to assess vomiting, diarrhea, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain and to record the symptoms in the e-diary. The symptoms will be assessed by the subject as absent, mild, moderate, or severe according to the grading scale in [Table 3](#). Only an investigator or medically qualified person is able to classify a subject's systemic events as Grade 4. If a subject experiences a suspected Grade 4 systemic event, the investigator must immediately notify the sponsor. If a subject experiences a confirmed Grade 4 systemic event determined to be related to the administration of the investigational product, further vaccinations will be discontinued in that subject. Further, if a systemic event persists beyond the end of the e-diary period following vaccination, the subject will be requested to report that information and any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF.

**Table 3. Systemic Event Grading Scale**

	<b>Mild (Grade 1)</b>	<b>Moderate (Grade 2)</b>	<b>Severe (Grade 3)</b>	<b>Grade 4</b>
<b>Vomiting</b>	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
<b>Diarrhea</b>	2-3 loose stools in 24 hours	4-5 loose stools in 24 hours	≥6 loose stools in 24 hours	Emergency room visit or hospitalization
<b>Headache</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
<b>Fatigue/ Tiredness</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
<b>New or worsening muscle pain</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
<b>New or worsening joint pain</b>	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization

Abbreviation: IV = intravenous.

#### 7.1.1.4. Fever

In order to record information on fever, a digital thermometer will be given to the subject with instructions on how to measure oral temperature at home. Temperature will be collected in the e-diary in the evening daily during the e-diary reporting period. It will also be collected at any time during the e-diary data collection periods that fever is suspected. If a fever persists beyond the end of the e-diary period following vaccination, the subject will be requested to report that information and any new AEs that develop to the investigator. The investigator will enter this additional information in the CRF. Fever is defined as an oral temperature of  $\geq 38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ). The highest temperature for each day will be recorded in the e-diary. In the event of a fever, temperature will be collected daily until fever has resolved (1 day of temperature less than  $38.0^{\circ}\text{C}$  [ $100.4^{\circ}\text{F}$ ]). Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 4.

**Table 4. Scale for Fever**

<b>Mild (Grade 1)</b>	38.0-38.4°C (100.4-101.1°F)
<b>Moderate (Grade 2)</b>	38.5-38.9°C (101.2-102.0°F)
<b>Severe (Grade 3)</b>	39.0-40.0°C (102.1-104.0°F)
<b>Grade 4</b>	>40.0°C ( $>104.0^{\circ}\text{F}$ )

If a subject experiences a confirmed Grade 4 fever determined to be related to the administration of the investigational product, further vaccinations will be discontinued in that subject.

### 7.1.2. Triggered Safety Data Review Rule

In light of the occurrence of cases of Grade 3 injection site erythema in subjects receiving a different formulation of the *C difficile* vaccine on a Day 1, 8, and 30 regimen (Section 1.2.3), a triggered safety data review rule will apply during the course of the study for e-diary-prompted injection site erythema. This is designed to trigger if the estimated lower limit of the 1-sided 97.5% CI around the rate of Grade 3 injection site erythema is greater than 2.1% among recipients of active vaccine.

The rule will be assessed in a blinded manner and will apply separately to each dose of vaccine (ie, Doses 1, 2, and 3) and each vaccination regimen (ie, Day 1, 8, and 30 or Month 0, 1, and 6), irrespective of vaccine allocation. The rule will not be applied to the fourth dose during the extension stage. E-diary data confirmed to be entered by the subject in error will not contribute towards the rule.

The triggered safety data review rule will have been met if 1 confirmed case of Grade 4 injection site erythema is reported. If more than 1 confirmed case of Grade 3 injection site erythema is reported, the rule will be assessed as follows. The number of confirmed cases (occurring after the specified dose number in the specified vaccination regimen) will be compared with the total number of subjects who have received the specified dose number in the specified vaccination regimen (in the knowledge that approximately 1 of 7 subjects will have received placebo). If the total number of subjects is less than or equal to the corresponding value shown in Table 5, the triggered safety data review rule will have been met.

**Table 5. Triggered Safety Data Review Rule Criteria for Grade 3 Injection Site Erythema After the Specified Dose Number in the Specified Vaccination Regimen**

Number of Confirmed Case(s) of Grade 3 Injection Site Erythema	Number of Subjects Having Received the Specified Dose Number in the Specified Vaccination Regimen
1	Rule does not apply
2	14
3	35
4	63
5	94
6	126
7	161
8	199
9	236
10	276
11	315
12	355
13	397
14	427

If the rule is met, the Pfizer IRC will conduct an expedited review of the available safety data in an unblinded manner to determine whether enrollment of new subjects to the impacted

vaccination regimen and administration of study injections to subjects already enrolled in the impacted vaccination regimen should be halted temporarily or whether any other measures should be taken to ensure subject safety. If the IRC determines that enrollment and vaccination in the impacted regimen should be halted temporarily, the data will also be reviewed by the E-DMC. Enrollment and vaccination of subjects in the impacted vaccination regimen will not recommence until the E-DMC evaluates all available safety data and provides recommendations and the sponsor notifies sites that these activities may continue (refer to [Section 9.5](#)). In the meantime, all other routine study conduct activities such as ongoing data entry, reporting of AEs, subject e-diary completion, and subject follow-up must continue. If only 1 vaccination regimen is impacted by the triggered safety data review rule, enrollment and vaccination in the other vaccination regimen will continue per protocol.

## 7.2. Immunogenicity

Serum samples will be obtained for immunogenicity testing as follows:

- For subjects assigned to the Day 1, 8, and 30 regimen, on Day 1, Day 8, Day 15, Day 30, Day 37, Month 2, Month 4, Month 7, and Month 13.
- For subjects assigned to the Month 0, 1, and 6 regimen, on Day 1, Day 30, Day 37, Month 2, Month 6, Day 187, Month 7, Month 12, and Month 18.
- During the extension stage: at the fourth dose (immediately before the fourth dose), on Days 8 and 30 after the fourth dose, and at Months 6, 12, 18, 24, 30, and 36 after the fourth dose.

Both toxin A– and toxin B–specific neutralizing antibody levels will be measured. A minimum of 10 mL and up to 20 mL of blood will be collected (prior to vaccination if at a vaccination visit) for each measurement to allow for adequate volume required for repeat testing or additional antigen-specific immunogenicity testing to be performed.

An additional blood sample of approximately 40 mL will be obtained at Visit 6 (Month 2) for subjects on the Day 1, 8, and 30 regimen and Visit 4 (Month 2) for subjects on the Month 0, 1, and 6 regimen for use in development, qualification, and validation of *C difficile* serologic assays and reagents.

An additional optional whole blood sample of approximately 20 to 50 mL will be obtained from subjects at designated sites for exploratory purposes as follows:

- Designated sites participating in the month regimen will be asked to obtain additional blood samples from subjects who have signed an additional ICD for this procedure at Visit 12 for exploratory purposes.

Refer to the SRM for details regarding serum sample management and storage.

**7.3. CCI**



CCI



## **8. ADVERSE EVENT REPORTING**

### **8.1. Adverse Events**

All observed or volunteered AEs regardless of vaccine group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

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

### **8.2. Reporting Period**

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including Visit 8 (Month 7 for subjects on the Day 1, 8, and 30 regimen and Month 12 for subjects on the Month 0, 1, and 6 regimen).

During the extension stage, the active reporting period for SAEs to Pfizer or its designated representative begins from the time that the subject provides informed consent for the extension stage, which is obtained prior to the subject's participation in the extension stage, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including Visit 12 (6 months after the fourth dose).

SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

All AEs should be recorded on the CRF from the time the subject provides informed consent until 1 month after the third vaccination (Visit 6 [Month 2] for subjects on the Day 1, 8, and 30 regimen and Visit 7 [Month 7] for subjects on the Month 0, 1, and 6 regimen).

During the extension stage, all AEs should be recorded on the CRF from the time the subject provides informed consent until 1 month after the fourth vaccination (Visit 11).

Any AE occurring up to 48 hours after each subsequent blood draw (Visit 6 [Month 2], Visit 7 [Month 4], Visit 8 [Month 7], and Visit 9 [Month 13] for subjects on the Day 1, 8, and 30 regimen and Visit 7 [Month 7], Visit 8 [Month 12], and Visit 9 [Month 18] for subjects on the Month 0, 1, and 6 regimen) must be recorded on the CRF.

During the latter part of the extension stage, any AE (including RRIs) occurring up to 48 hours after the blood draw at Visits 12, 13, 14, 15, 16, and 17 (Months 6, 12, 18, 24, 30, and 36 after the fourth dose) must be recorded on the CRF.

The investigator is required to assess whether the AE may be related to the subject's participation in the study.

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### **8.3. Definition of an Adverse Event**

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.



Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

#### **8.4. Medication Errors**

Medication errors may result, in this study, from the administration of the wrong investigational product, to the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

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

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

Other examples include, but are not limited to:

- The administration of expired investigational product;
- The administration of an incorrect investigational product;
- The administration of an incorrect dosage;

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

### **8.5. Abnormal Test Findings**

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

### **8.6. Serious Adverse Events**

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Lack of efficacy in an approved indication should be reported as an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### **8.6.1. Protocol-Specified Serious Adverse Events**

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

### **8.6.2. Potential Cases of Drug-Induced Liver Injury**

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values  $\geq 3$  times the upper limit of normal ( $\times$  ULN) concurrent with a total bilirubin value  $\geq 2 \times$  ULN with no evidence of hemolysis and an alkaline phosphatase value  $\leq 2 \times$  ULN or not available;
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
  - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values  $\geq 2$  times the baseline values and  $\geq 3 \times$  ULN, or  $\geq 8 \times$  ULN (whichever is smaller).

Concurrent with

- For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least  $1 \times$  ULN **or** if the value reaches  $\geq 3 \times$  ULN (whichever is smaller).

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

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

### **8.7. Research-Related Injury**

During the latter part of the extension stage, for up to 48 hours after the blood draw at Visits 12, 13, 14, 15, 16, and 17 (Months 6, 12, 18, 24, 30, and 36 after the fourth dose), should a subject, in the investigator's opinion, suffer a medically important RRI caused by his or her participation in the protocol, Pfizer or its representative must be informed immediately.

A medically important RRI is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as an RRI.

An investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury

in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

## **8.8. Hospitalization**

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

### 8.9. Severity Assessment

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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 8.10. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as

appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

### **8.11. Exposure During Pregnancy**

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

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

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

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

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

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

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

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

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

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

## **8.12. Occupational Exposure**

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

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

## **8.13. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)**

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

## **8.14. Eliciting Adverse Event Information**

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

## **8.15. Reporting Requirements**

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

### **8.15.1. Serious Adverse Event Reporting Requirements**

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

If the investigator is aware of an SAE following investigational product administration, the investigator must contact the Pfizer study physician directly immediately after sending the SAE report form to Pfizer as described above. These procedures do not replace any of the standard AE reporting requirements as described above. Additional information regarding such events and the reporting requirements are included in the SRM.

### **8.15.2. Nonserious Adverse Event Reporting Requirements**

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

### **8.15.3. Sponsor's Reporting Requirements to Regulatory Authorities**

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## **9. DATA ANALYSIS/STATISTICAL METHODS**

Detailed methodology for summary and statistical analysis of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be finalized before the start of any analyses and will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint

definition and/or its analysis will be reflected both in the amended protocol and in the SAP. The SAP amendment will follow the protocol amendment.

### 9.1. Sample Size Determination

The study sample size is not based on statistical hypothesis test considerations. All statistical analyses will be descriptive in nature. An estimation approach will be used to assess the safety and immunogenicity objectives in the study.

Sample size information for the primary immunogenicity endpoint is included in Table 6. If it is assumed that the true proportion of subjects with neutralizing antibody levels greater than the specified threshold is 70% and study dropout rate is at most 12%, 183 subjects per vaccine group would yield 161 evaluable subjects per vaccine group, giving the study at least 80% power to demonstrate the proportion is 59.2% or greater (by the lower bound of a 2-sided 95% confidence limit based on an exact method for 1-sample binomial proportion). If the proportion of subjects with neutralizing antibody levels greater than the specified threshold is assessed in the subset of study participants who are seronegative at baseline (before Dose 1), estimated to be at least 103 subjects per group, the study will have at least 80% power to demonstrate that the proportion is 56.0% or greater, assuming a maximum discontinuation rate of 12% and a baseline seronegativity rate of 64% (estimated from the toxin B-specific neutralizing antibody levels from Study B5091001). Additionally, [Table 7](#) presents the precisions of the 2-sided 95% CI for neutralizing antibody mean concentration (in log10) with sample sizes of 103, 161, and 183 with the assumed standard deviations (SDs).

**Table 6. Minimum Detectable Proportion of Subjects With the Specified Antibody Levels (Primary Immunogenicity Endpoint)**

Assumed True Proportion	Evaluable Subjects Per Group	Minimum Detectable Proportion of Subjects With Specified Antibody Level(s) With at Least	
		80% Power	90% Power
0.70	183	59.9%	58.2%
	161	59.2%	57.3%
	103	56.0%	54.0%

Note: All calculations are based on lower bound of 2-sided 95% confidence limit of the exact method for 1-sample binomial proportion.

**Table 7. Precision of the 2-Sided 95% Confidence Interval for Neutralizing Antibody Mean Concentration (in Log10)**

Assumed True SD <sup>a</sup> (in Log10)	Z0.025 (for 95% CI)	Precision of 2-Sided 95% CI <sup>b</sup>		
		N = 103	N=161	N=183
0.40	1.96	0.077	0.062	0.058
0.50	1.96	0.097	0.077	0.072
0.60	1.96	0.116	0.093	0.087
0.70	1.96	0.135	0.108	0.101
0.90	1.96	0.174	0.139	0.130
1.10	1.96	0.212	0.170	0.159
1.30	1.96	0.251	0.201	0.188
1.50	1.96	0.290	0.232	0.217
2.00	1.96	0.386	0.309	0.290

a. Based on immunogenicity results from Study B5091001, the standard deviation (SD) of the neutralization titer after log10 transformation from Study B5091001 for the 100- $\mu$ g *C difficile* + aluminum hydroxide vaccine and 200- $\mu$ g *C difficile* + aluminum hydroxide vaccine groups ranges from 0.41 to 0.62 for toxin A and from 0.78 to 1.40 for toxin B at the Day 37 and Month 7 visits, and from 0.38 to 0.55 for toxin A and from 0.35 to 1.77 for toxin B if excluding data from seropositive subjects at baseline.

b. Precision is the distance from the mean to the confidence limit expressed in log10 of neutralization units/mL.

For safety outcomes, Table 8 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, at various sample sizes. For example, if a true AE event rate is 1.0%, the probability of observing at least 1 such AE is 0.84 in a vaccine group of 183 subjects.

**Table 8. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes**

Assumed True Event Rate of an AE	N=183	N=366	N=732
<b>0.50%</b>	0.60	0.84	0.97
<b>0.70%</b>	0.72	0.92	0.99
<b>0.80%</b>	0.77	0.95	>0.99
<b>0.90%</b>	<b>0.81</b>	0.96	>0.99
<b>1.0%</b>	0.84	0.97	>0.99
<b>1.5%</b>	0.94	>0.99	>0.99
<b>2.0%</b>	0.98	>0.99	>0.99
<b>2.5%</b>	0.99	>0.99	>0.99
<b>5.0%</b>	>0.99	>0.99	>0.99

## 9.2. Immunogenicity Analysis

The immunogenicity data will be summarized according to the vaccine group as randomized. For any *C difficile* toxin A– or toxin B–specific neutralizing antibody level that is below the lower limit of quantitation (LLOQ), the lower limit of detection (LOD), defined as  $0.5 \times$  LLOQ, will be assigned. No other missing assay data will be imputed in the analyses. All immunogenicity analyses will be performed after the imputation of the antibody levels that are below the LLOQ.

For the immunogenicity analysis, subjects will be analyzed separately for each planned dosing regimen (Days 1, 8, and 30 or Months 0, 1, and 6) for each stage (original planned stage [first 3 vaccinations] and extension stage [fourth vaccination]). This applies to all analyses outlined in [Section 9.2.2](#) and [Section 9.2.3](#).

### 9.2.1. Immunogenicity Analysis Population

An evaluable immunogenicity population and a modified intent-to-treat (mITT) population for each stage (original planned stage [first 3 vaccinations] and extension stage [fourth vaccination]) will be defined for the immunogenicity analyses separately. The evaluable immunogenicity populations will be the primary populations for the immunogenicity analyses.

In general, the evaluable immunogenicity population will include all subjects who are eligible, receive the investigational product to which they are randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for the proposed analysis, and have no major protocol violations. The mITT population will include all randomized subjects who have at least 1 valid and determinate assay result for the proposed analysis.

### 9.2.2. Analysis of the Primary Immunogenicity Endpoint

The primary immunogenicity endpoints are the proportions of subjects with toxin A–, toxin B–, and both toxin A– and toxin B–specific neutralizing antibody levels (neutralization units/mL)  $\geq$  the specified threshold(s) at Day 37 (7 days after Dose 3 for subjects receiving the Day 1, 8, and 30 regimen) and at Month 7 (1 month after Dose 3 for subjects receiving the Month 0, 1, and 6 regimen). Point estimates and associated 2-sided 95% exact CIs will be descriptively summarized for each vaccine group.

### 9.2.3. Analysis of the Secondary and Other Immunogenicity Endpoints

GMCs of the toxin A– and toxin B–specific neutralizing antibody levels at each blood sampling time point will be descriptively summarized for each vaccine group, along with associated 2-sided 95% CIs. The CIs will be constructed by back transformation of the confidence limits computed for the mean of the logarithmically transformed assay data based on Student t distribution.

Point estimates and the associated 2-sided 95% exact CIs will be descriptively summarized for each vaccine group for the following immunogenicity endpoints:

1. Proportions of subjects with toxin A–, toxin B–, and both toxin A– and toxin B–specific neutralizing antibody levels (neutralization units/mL)  $\geq$  the specified threshold(s) at each blood sampling time point except for Day 37 (7 days after Dose 3 for subjects receiving the Day 1, 8, and 30 regimen) and Month 7 (1 month after Dose 3 for subjects receiving the Month 0, 1, and 6 regimen).
2. Proportions of subjects with  $\geq$ 4-fold,  $\geq$ 8-fold,  $\geq$ 16-fold, and  $\geq$ 32-fold rises in either toxin A–, toxin B–, or both toxin A– and toxin B–specific neutralizing antibody levels compared to baseline at each postbaseline blood sampling time point.

The GMFRs in toxin A– and toxin B–specific neutralizing antibody levels from before vaccination to after vaccination will be summarized for each vaccine group by geometric means and associated 95% CIs at all postbaseline blood sampling time points. These CIs are also computed by back transformation of the CIs using the Student t distribution for mean difference of measures on the logarithmically transformed assay results (postvaccination relative to prevaccination).

Empirical reverse cumulative distribution curves (RCDCs) will be presented for each toxin A– and toxin B–specific antibody level.

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### 9.3. Safety Analysis

The safety population will include all subjects who receive at least 1 dose of an investigational product. For the safety analysis, subjects will be analyzed according to the investigational product received. For each stage (original planned stage [first 3 vaccinations] and extension stage [fourth vaccination]), all safety data will be analyzed separately for each planned dosing regimen (Days 1, 8, and 30 or Months 0, 1, and 6).

AEs will be categorized according to MedDRA and will be summarized by vaccine group. All summaries of AEs will show the number and percentage of subjects experiencing at least 1 event and the number of events for each vaccine group.

The proportion of subjects reporting local reactions at the injection site and systemic events on any day within the 7- to 14-day period after vaccination will be descriptively summarized by vaccine group. Severities of local reactions and systemic events reported after each vaccination will also be descriptively summarized by vaccine group. Two-sided exact 95% CIs will be presented with the proportions.

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### 9.4. Analysis Timing

Six analyses, described below, will be performed for this study.

As there is no formal statistical hypothesis test conducted for the protocol and all statistical analyses are descriptive in nature, and the study will not be terminated because of favorable results at any of the analyses, there will be no formal multiplicity adjustments applied in all analyses. All CIs will be created at nominal level without multiplicity adjustments.

Before the first analysis is initiated, the details of the objectives, decision criteria, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an IRC charter and the detailed statistical analysis plan documented and approved in an SAP.

#### **9.4.1. First Interim Analysis**

The first interim analysis is planned for the study when Month 2 data are available from all continuing subjects. All available immunogenicity and safety data will be included in this analysis.

The objective of the first analysis is to determine the suitability of the Day 1, 8, and 30 regimen for further study.

#### **9.4.2. Second Interim Analysis**

The second interim analysis is planned for the study when Month 7 data are available from approximately the first 700 continuing subjects. All available immunogenicity and safety data will be included in this analysis.

The objective of the second analysis is to inform internal program-level decision making.

#### **9.4.3. Third Interim Analysis**

The third interim analysis is planned for the study when Month 7 data are available from all continuing subjects. All available immunogenicity and safety data will be included in this analysis.

The objective of the third analysis is to determine the suitability of the Month 0, 1, and 6 regimen for further study and to select the optimal vaccine dose level for further study.

#### **9.4.4. Fourth Interim Analysis**

The fourth interim analysis will be conducted when 6 months post-Dose 3 data are available from all continuing subjects (Month 7 for subjects receiving the Day 1, 8, and 30 regimen and Month 12 for subjects receiving the Month 0, 1, and 6 regimen). All available immunogenicity and safety data will be included in this analysis.

The objective of the fourth analysis is to support regulatory interactions.

#### **9.4.5. Analysis for the Primary Clinical Study Report**

The analysis for the primary clinical study report (CSR) will be performed when all subjects have completed Visit 9 and all immunogenicity and safety data up to and including Visit 9

are available. No multiplicity adjustments will be made on the descriptive analyses. All CIs will be created at nominal level in this analysis.

#### **9.4.6. Analysis During the Extension Stage**

No formal interim analyses are planned for the extension stage. Safety and immunogenicity data will be descriptively summarized periodically in order to protect the safety of subjects and to support internal program-level decision making.

The analysis for the supplemental CSR will be performed when all extension-stage immunogenicity and safety data up to Visit 17 are available for subjects who entered the extension stage. No multiplicity adjustments will be made on the descriptive analyses. All CIs will be created at nominal level in this analysis.

#### **9.5. Data Monitoring Committee**

This study will utilize a Pfizer IRC, which will be responsible for reviewing data in the event the triggered safety data review rule is met and also to review the results of the 4 planned interim analyses. The IRC will be composed of senior Pfizer Vaccine Research & Development personnel, not directly involved with the study conduct, which serves to make recommendations based on safety findings or the results of the interim analyses. These could include advance ordering of future clinical trial supplies or an administrative increase in the number of subjects enrolled by a maximum of 30%.

In addition, the study will use an E-DMC independent of Pfizer. The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study, including review of unblinded data according to the charter. The E-DMC is scheduled to hold regular review meetings approximately twice a year to review safety results. Additional ad hoc E-DMC meetings will be held as needed. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

### **10. QUALITY CONTROL AND QUALITY ASSURANCE**

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

### **11.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant

correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

### **12.1. Institutional Review Board/Ethics Committee**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

### **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

### **12.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site

will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject's personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

#### **12.4. Subject Recruitment**

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

#### **12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### **13. DEFINITION OF END OF TRIAL**

The end of trial in all participating countries is defined as last subject last visit (LSLV), ie, when the final subject completes Visit 17 in the extension stage.

### **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of *C difficile* vaccine at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 2 weeks. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## **15. PUBLICATION OF STUDY RESULTS**

### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT) and/or [www.pfizer.com](http://www.pfizer.com), and other public registries in accordance with applicable local laws/regulations.

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

#### **[www.clinicaltrials.gov](http://www.clinicaltrials.gov)**

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

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

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#### **[www.pfizer.com](http://www.pfizer.com)**

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on [www.pfizer.com](http://www.pfizer.com) for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

## **15.2. Publications by Investigators**

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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## Appendix 1. Abbreviations

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
<i>C difficile</i>	<i>Clostridium difficile</i>
CBER	Center for Biologics Evaluation and Research
CDAD	<i>C difficile</i> –associated diarrhea
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
DAI	dosage and administration instructions
DMARD	disease-modifying antirheumatic drug
EC	ethics committee
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	enzyme-linked immunosorbent assay
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FIH	first-in-human
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMFR	geometric mean fold rise
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
IC <sub>50</sub>	50% inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device

Abbreviation	Term
LFT	liver function test
LLOQ	lower limit of quantitation
LOD	limit of detection
LSLV	last subject last visit
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
NHP	nonhuman primate
PT	preferred term
RCDC	reverse cumulative distribution curve
RRI	research-related injury
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
TcdA	<i>C difficile</i> toxin A
TcdB	<i>C difficile</i> toxin B
ULN	upper limit of normal
US	United States

## Document Approval Record

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Signed By:	Date(GMT)	Signing Capacity
PPD	24-Apr-2017 13:47:34	Business Line Approver
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