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

Investigational Product Number:	PF-06425090
Investigational Product Name:	*Clostridium difficile* Vaccine
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	CCI [redacted]
Protocol Number:	B5091019
Phase:	3

Short Title: *C difficile* Vaccine 2- Versus 3-Dose Noninferiority Study

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Protocol Amendment 1	02 May 2019	Following regulatory consultation, the following were added: • A coprimary estimand of seroresponse difference at Month 7. • A secondary estimand of the seroresponse difference at Month 12. • A noninferiority comparison of dosing regimens by age group. Increased the number of participants to support the analysis for the coprimary immunogenicity estimands in order to meet the study's primary immunogenicity objective. The enrollment period has been extended to allow for the recruitment of the additional participants; therefore, the study duration has also increased. Added a visit at Month 9 for immunogenicity blood draw to provide more information on the immune response over time.
Original protocol	18 October 2018	Not applicable (N/A)

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

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1. PROTOCOL SUMMARY

1.1. Synopsis

Indication

Pfizer's investigational *Clostridium difficile* vaccine (PF-06425090) is a prophylactic vaccine that is currently being investigated for the prevention of primary *C difficile* infection (CDI) in adults 50 years of age and older.

Objectives, Estimands, and Endpoints

Primary Immunogenicity Objective	Coprimary Immunogenicity Estimands	Primary Immunogenicity Endpoint
• To demonstrate the noninferiority of a 2-dose regimen of the *C difficile* vaccine compared to a 3-dose regimen of the *C difficile* vaccine.	• For each of toxin A– and toxin B–specific neutralizing antibody levels: Adjusted geometric mean concentration (GMC) ratio, estimated by the ratio of the adjusted GMC (adjusted for baseline concentration) for the 2-dose regimen to the adjusted GMC for the 3-dose regimen, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). • For each of toxin A– and toxin B–specific neutralizing antibody levels: Seroresponse difference, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). Seroresponse for each of toxin A– and toxin B– specific neutralizing antibody levels: For both seronegative (baseline concentration < lower limit of quantitation [LLOQ]) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from the baseline neutralizing antibody	• *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 7 in each regimen.

	level following vaccination.	
Primary Safety Objective	**Primary Safety Estimands**	**Primary Safety Endpoints**
• To evaluate the safety of *C difficile* vaccine when administered to participants in a 2-dose regimen or a 3-dose regimen by assessing local reactions and systemic events, adverse events (AEs), and serious adverse events (SAEs).	• In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting local reactions. • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting systemic events. • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting nonserious AEs. • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting SAEs.	• Local reactions (pain, erythema, and induration), as self-reported on e-diaries for up to 7 days following each dose of investigational product in each regimen. • Systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain), as self-reported on e-diaries for up to 7 days following each dose of investigational product in each regimen. • Nonserious adverse events from signing of the informed consent document (ICD) to 1 month after receipt of the last dose of investigational product in each regimen. • SAEs from signing of the ICD to 6 months after receipt of the last dose of investigational product in each regimen.

Secondary Objective	Secondary Estimands	Secondary Endpoint
• To demonstrate the noninferiority of a 2-dose regimen of the *C difficile* vaccine compared to a 3-dose regimen of the *C difficile* vaccine.	• For each of toxin A– and toxin B–specific neutralizing antibody levels: Adjusted GMC ratio, estimated by the ratio of the adjusted GMC (adjusted for baseline concentration) for the 2-dose regimen to the adjusted GMC for the 3-dose regimen, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). • For each of toxin A– and toxin B–specific neutralizing antibody levels: Seroresponse difference, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). Seroresponse for each of toxin A– and toxin B– specific neutralizing antibody levels: For both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from the baseline neutralizing antibody level following vaccination.	• *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 12 in each regimen.

Overall Design

This is a Phase 3, randomized, observer-blinded study to evaluate the immunogenicity, safety, and tolerability of a 2-dose regimen of *C difficile* vaccine compared to a 3-dose regimen of *C difficile* vaccine in adults 50 years of age and older.

Participants will be randomly assigned in parallel in a 1:1 ratio to receive *C difficile* vaccine (200 µg total toxoid) at Months 0, 1, and 6 (3-dose group) or at Months 0 and 6 (2-dose group). The participants in the 2-dose group will receive placebo (saline) at Month 1.

Investigational Products

Clostridium difficile Vaccine

The investigational *C difficile* vaccine is toxoid based. *C difficile* toxin A and toxin B are inactivated by a combination of genetic mutations and chemical treatments. CCI [redacted]

Placebo (2-Dose Regimen Only)

The placebo will consist of a sterile normal saline solution for injection (0.9% sodium chloride injection, in a 0.5-mL dose) in a prefilled syringe (PFS) and will be provided by the sponsor to each study site.

Number of Participants

Approximately 1960 participants will be randomized into the study, such that approximately 1568 (784 per vaccine group) evaluable participants complete the study.

CCI [redacted]

Statistical Methods

The study sample size estimate is based on the evaluation of the primary immunogenicity objective of the study to demonstrate that the immune responses induced by 2 doses of *C difficile* vaccine (administered in a 0- and 6-month regimen) are noninferior to the immune responses induced by 3 doses of *C difficile* vaccine (administered in a 0-, 1-, and 6-month regimen) —by evaluating the toxin A– and toxin B–specific neutralizing antibody in terms of GMC ratios and the difference in percentage of participants achieving seroresponse, 1 month after the last investigational product administration. Seven hundred and eighty-four (784) evaluable participants per group will provide an overall power of 90.5% to meet the primary objective of noninferiority of a 2-dose to a 3-dose regimen for both toxin A and toxin B, 1 month after the last dose. The primary immunogenicity objective of noninferiority of the 2-dose regimen compared with the 3-dose regimen will be achieved if (1) the lower limit of the 2-sided 95% confidence interval (CI) for the GMC ratio (2-dose/3-dose regimen) is >0.67 for both toxin A and toxin B, and (2) the lower limit of the 2-sided 95% CI for the difference in percentage of participants achieving seroresponse (2-dose minus 3-dose regimen) is > -10% for both toxin A and toxin B 1 month after the last vaccination. The same criteria will be used for the secondary immunogenicity objective evaluation, which will be conducted only after the primary immunogenicity objective is met.

Assuming a maximum study nonevaluable rate of 20% and a randomization ratio of 1:1, a total of 1960 participants need to be randomized in the study to meet the primary immunogenicity objectives.

For each of toxin A– and toxin B–specific neutralizing antibody levels, the GMC ratio of the 2-dose regimen to the 3-dose regimen at Month 7 and Month 12 will be evaluated by an analysis of covariance (adjusted for baseline antibody concentrations) and the corresponding 95% CIs. Two (2)-sided 95% CIs will be constructed by obtaining a CI for the mean of the logarithmically transformed assay results based on the Student t distribution, and transforming the confidence limits back to the original units. For each of the toxin A– and toxin B–specific neutralizing antibody levels, the difference between the 2-dose and 3-dose regimens in the percentage of participants achieving seroresponse at Month 7 and Month 12 will be computed, along with 95% CIs, using the Miettinen and Nurminen method. Seroresponse will be considered achieved if a participant has at least a 4-fold rise from baseline in the respective antibody concentration following vaccination. Baseline concentration is defined as the antibody concentration results from the blood drawn before vaccine Dose 1. Antibody concentration values below the LLOQ or denoted as below the limit of quantitation (BLQ) will be set to 0.5 × LLOQ for analysis.

All safety and reactogenicity endpoints will be summarized as proportions of participants with events by vaccine group. Additionally, exact 2-sided 95% CIs for proportions will be calculated using the Clopper-Pearson method.

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Visit Description	**Month 0 (Vax 1)**	**Month 1 (Vax 2)**	**Month 2 (Telephone Contact)**	**Month 6 (Vax 3)**	**Month 7**	**Month 9**	**Month 12 (End of Study)**
Visit Window (Days)	**1**	**28-42 Days After Visit 1**	**28-42 Days After Visit 2**	**140-168 Days After Visit 2**	**28-42 Days After Visit 4**	**84-98 Days After Visit 4**	**165-195 Days After Visit 4**
Informed consent[a]	X						
Demography[a]	X						
Clinical assessment, including medical history[a]	X						
Record nonstudy vaccinations[b]	X	X	X	X	X		
Measure and record height and weight[a]	X						
Oral temperature[a]	X	X		X			
Urine pregnancy test (women of childbearing potential)[a]	X	X		X			
Discuss contraceptive use[b]	X	X	X	X			
Confirm eligibility[b]	X	X	X	X	X	X	
Review temporary delay criteria[a]	X	X		X			
Randomization[a]	X						
Blood draw for immunogenicity assessment[b]	20 mL			20 mL	20 mL + 40 mL[c]	20 mL[d]	20 mL[d]
Vaccination	X	X		X			
Postvaccination observation (30 minutes) and AE assessment	X	X		X			

Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Visit Description	**Month 0 (Vax 1)**	**Month 1 (Vax 2)**	**Month 2 (Telephone Contact)**	**Month 6 (Vax 3)**	**Month 7**	**Month 9**	**Month 12 (End of Study)**
Visit Window (Days)	**1**	**28-42 Days After Visit 1**	**28-42 Days After Visit 2**	**140-168 Days After Visit 2**	**28-42 Days After Visit 4**	**84-98 Days After Visit 4**	**165-195 Days After Visit 4**
Issue e-diary, measuring device, and thermometer and provide instructions on their use, as required	X	X		X			
Record AEs	X ◄----	----X----	----X----	----X----	----► X	X[d]	X[d]
Record SAEs	X ◄----	----X----	----X----	----X----	----X----	----X----	----► X
Telephone contact			X				
Participant completes e-diary	X ◄----	----X----	----------	----X----►			
Review e-diary data[e]							
Collect e-diary					X		

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

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

2. INTRODUCTION

2.1. Study Rationale

The purpose of the study is to evaluate the immunogenicity, safety, and tolerability of a 2-dose regimen of the *C difficile* vaccine compared to a 3-dose regimen of the *C difficile* vaccine in adults 50 years of age and older. The study will recruit participants who may be at increased risk for developing CDI, and the study population, inclusion criteria, and exclusion criteria will be consistent with those of the Phase 3 B5091007 efficacy study, allowing direct immunological comparison. Vaccine compliance (completion of a 3-dose vaccine series) has been challenging as evidenced, as an example, by human papillomavirus (HPV) 9 vaccine.[1] It is expected that this would be especially challenging with a 3-dose vaccine regimen given in an adult population, which could have public health consequences. The *C difficile* vaccine program utilizes a 3-dose vaccine regimen at Months 0, 1, and 6 with a 200-µg dose. The 200-µg month regimen in our Phase 2 B5091009 study, our ongoing B5091007 efficacy study, and our B5091008 lot-consistency study utilize this regimen and dose.

A 2-dose vaccine regimen would presumably improve compliance. This study, therefore, will be a noninferiority study comparing a 3-dose regimen (Months 0, 1, and 6) with a 2-dose regimen (Months 0 and 6).

2.1.1. Mechanism of Action/Indication

Pfizer's investigational *C difficile* vaccine (PF-06425090) is a prophylactic vaccine that is currently being investigated for the prevention of primary CDI in adults 50 years of age and older.

2.2. Background

2.2.1. *Clostridium difficile* Disease Background

C difficile, a gram-positive, anaerobic, spore-forming bacillus, is the main cause of nosocomial infectious diarrhea in industrialized countries.[2,3,4,5,6] It accounts for 20% to 30% of cases of antibiotic-associated diarrhea and is the most commonly recognized cause of infectious diarrhea in healthcare settings.[7] *C difficile* is carried in approximately 3% of healthy adults and approximately 16% to 35% of hospital inpatients; among the latter, the rate increases with exposure to antibiotics.[8] As many as 50% or more of hospital patients colonized by *C difficile* are asymptomatic carriers.[7]

C difficile can produce 3 toxins, toxin A (TcdA), toxin B (TcdB), and binary toxin.[9] TcdA and TcdB are the principal virulence factors for CDI,[10] causing severe inflammation in the bowel.[11,12] The spectrum of CDI ranges from asymptomatic colonization and mild self-limiting diarrhea, to more serious complications such as severe diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation, and death.[3,13]

Individuals with mild to moderate CDI may experience diarrhea 3 or more times a day for 2 or more days, along with mild abdominal cramping and tenderness. However, individuals with a severe infection may experience watery diarrhea 10 to 15 times a day, abdominal cramping and pain that may be severe, fever, blood or pus in the stool, nausea, dehydration, loss of appetite, weight loss, swollen abdomen, kidney failure, and increased white blood cell count.[14]

The main risk factors for an initial episode of CDI are antibiotic therapy, prolonged hospitalization, and severe comorbidities. Older adults (>65 years of age) are at an increased risk for CDI, particularly when exposed to healthcare settings.[12,15,16,17,18] Although most patients experiencing a first episode of CDI respond well to standard antibiotic treatment, approximately 15% to 35% of patients suffer from at least 1 recurrence.[12,19,20] Additional risk factors for recurrence include failure to mount an immune response to TcdA and/or TcdB and infection with a hypervirulent strain.[21,22]

Increased incidence and severity of the disease with associated complications, colectomy rates, and mortality have been observed over the last 10 to 20 years.[23,24,25] In Europe, increased mortality, prolonged length of hospital stay, and incremental cost of hospitalization in association with CDI have been reported.[26,27] A systematic review published in 2012 reported 30-day mortality estimates in Europe ranging from 6.8% to 42%.[27] In a surveillance study conducted in the United States, approximately 453,000 cases of CDI and approximately 29,000 deaths were reported in 2011.[28] Based on data reported from acute care facilities, the cost of caring for patients experiencing CDI in the United States ranges from $1.1 to $4.8 billion annually.[29,30]

In the last decade, the numbers and severity of *C difficile* iatrogenic outbreaks in hospitals and nursing homes have increased.[28,29,31] Key factors in this escalation include emergence of hypervirulent pathogenic strains such as BI/NAP1/027,[32,33,34] increased use of antibiotics,[35] improved detection methods, and increased exposure to spores in healthcare facilities.[36]

Metronidazole has been recommended as initial therapy since the late 1990s, but recent guidance issued by Infectious Diseases Society of America (IDSA) recommends either vancomycin or fidaxomycin as the first choice, and only if not available should metronidazole be used.[7,22,37,38] Fidaxomicin has been developed more recently and has been shown to be noninferior to vancomycin for treatment of CDI. In addition, treatment with fidaxomicin was associated with a significantly lower rate of recurrence than was treatment with vancomycin.[20] European guidelines for treatment of CDI include fidaxomicin as an option for treatment of recurrence.[22] Fecal transplantation has also been shown to be effective in some patients for the treatment of multiple recurrences of CDI.[39,40] However, regulatory oversight of this method remains in development,[41] and, therefore, a highly effective noninvasive treatment for complicated CDI does not exist.

To date, the only measures available to help prevent CDI are behavioral ones such as encouraging appropriate use of antimicrobials, use of contact precautions, and cleaning and disinfection of equipment and the environment.[42]

2.2.2. *Clostridium difficile* Vaccine Development Rationale

The increasing burden of CDI on patients and on the healthcare system demonstrates that prevention of CDI constitutes a significant unmet medical need.

It is well established that 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 of antitoxin A and B immunoglobulin G (IgG) (as measured by enzyme-linked immunosorbent assay [ELISA]) and protection from CDI or recurrence after primary CDI.[21,43,44,45] Preclinical studies have shown that active immunization with inactivated toxins ("toxoids") and passive immunization with antitoxin antibodies protect animals from lethal challenge.[46,47,48] Furthermore, a Phase 2 trial with monoclonal antibodies (mAbs) designed to neutralize TcdA and TcdB provides clinical evidence supporting a role for antitoxin antibodies in the prevention of CDI recurrences.[49] Systemic administration of a combination of 2 neutralizing human mAbs against TcdA and TcdB was associated with fewer recurrences than placebo (7% versus 25% recurrences, respectively; $p<0.001$). These results were confirmed in 2 Phase 3 studies. In both studies, results showed that the rate of recurrence of CDI was significantly lower when the mAb against TcdB (bezlotoxumab) was administered, whether on its own or in combination with the mAb against TcdA (actoxumab), compared with placebo.[50] Finally, another group demonstrated that a combination of 2 mAbs directed against different epitopes from the binding domain of TcdA was significantly more potent in neutralizing the toxin in vitro than a single mAb.[51] Furthermore, while the TcdA and TcdB amino acid sequences are generally well conserved within the same sequence types, there is high variation between sequence types,[52] indicating that a polyclonal antibody approach, such as elicited by active immunization with *C difficile* toxoids, may be more efficacious to prevent primary and recurrent CDI. Taken together, these findings provide the rationale for the development of a *C difficile* toxoid-based vaccine to prevent CDI that includes both TcdA and TcdB. Pfizer therefore is developing a bivalent vaccine composed of both toxoids to elicit broad antitoxin immunity against TcdA and TcdB.

To date, there is no approved vaccine to prevent primary or recurrent CDI. There is at least 1 other vaccine in development that targets *C difficile* toxins. This is a recombinant fusion protein comprising fragments of the receptor-binding domains of TcdA and TcdB separated by a 4–amino acid linker[53]; this vaccine has been evaluated in a completed Phase 2 study.[54]

2.2.3. *Clostridium difficile* Vaccine Candidate

Pfizer's *C difficile* vaccine candidate consists of a 1:1 mixture of *C difficile* toxoids A and B. The toxoids were derived from native toxins by genetic modification to decrease toxin activity, and chemical inactivation prior to final purification and formulation of the drug substance.

2.2.3.1. Preclinical Development

In preclinical experiments, Pfizer's *C difficile* candidate vaccine was studied either alone or in combination with AlOH. Using the standard hamster *C difficile* disease model, vaccine formulations with and without AlOH demonstrated a survival benefit, providing at least 90% protection from a lethal challenge with *C difficile* spores in the immunized hamsters. In addition, pooled sera obtained from hamsters immunized with the *C difficile* vaccine formulated with AlOH neutralized secreted toxins from *C difficile* isolates representing diverse ribotypes/pulsed-field gel electrophoresis (PFGE) types, including hypervirulent strains, and covering >67% and >70% of the circulating strains in the United States and Europe, respectively. Furthermore, in nonhuman primates, Pfizer's toxoid vaccine formulations with and without AlOH induced robust neutralizing antitoxin antibody responses to both TcdA and TcdB. The preclinical data generated by Pfizer in rhesus macaques support the use of a 3-dose regimen of the *C difficile* vaccine, with or without AlOH.

2.2.3.2. Clinical Development

The B5091001 first-in-human study was a placebo-controlled, randomized, observer-blinded Phase 1 study that evaluated the safety, tolerability, and immunogenicity of Pfizer's *C difficile* vaccine. Three (3) antigen dose levels (50, 100, and 200 μg) were assessed and administered either alone or in combination with AlOH at Months 0, 1, and 6 to healthy adults 50 to 85 years of age.[55] Overall, the *C difficile* vaccine formulations and dose levels administered were generally well tolerated. Local reactions and systemic events were predominantly mild to moderate, were more common in the 50- to 64-year age cohort, and comprised mostly injection site pain, headache, and fatigue. AEs were reported in all vaccine groups, with little difference in the number of participants between the dose groups and the placebo group or between vaccine formulations. In participants who received the vaccine formulations, both the toxin A– and toxin B–specific neutralizing antibody GMCs increased substantially at 1 month after Dose 2 and after Dose 3 compared to baseline. In the 50- to 64-year age cohort, GMFRs in toxin A–specific neutralizing antibodies from baseline at Month 7 ranged from 59.19 to 149.23 in the dose groups compared to 2.47 in the control group. For toxin B–specific neutralizing antibodies, the GMFRs from baseline at Month 7 ranged from 116.67 to 2503.75 in the dose groups compared to 2.48 in the control group. In the 65- to 85-year age cohort, the GMFRs in toxin A–specific neutralizing antibodies from baseline at Month 7 ranged from 42.73 to 254.77 in the dose groups compared to 2.03 in the control group. For toxin B–specific neutralizing antibodies, the GMFRs from baseline at Month 7 ranged from 136.12 to 4922.80 in the dose groups compared to 1.58 in the control group. Potent antitoxin neutralizing responses were still evident in immunized participants in both age groups at Month 12. Although there was no clear dose-level response pattern, the data suggest that both the antitoxin A– and antitoxin B–specific neutralizing responses were trending higher in the toxoid-only groups compared to the toxoid + AlOH groups. Furthermore, the magnitude of the immune response was similar in the 2 age cohorts.

Study B5091003, a Phase 2 study, was conducted to assess 2 antigen dose levels (100 and 200 μg) of the toxoids alone reconstituted with sodium chloride (60 mM) diluent administered as a 3-dose regimen (Days 1, 8, and 30) in healthy adults 50 to 85 years of age. However, recruitment and vaccinations were halted because of the occurrence of 7 cases of Grade 3 injection site redness after Dose 2. Following the observed tolerability profile in Study B5091003, the decision was made to progress development of the aluminum-containing formulation into a second Phase 2 study, B5091009.

Study B5091009 (original planned stage up to 12 months after the third dose) was 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 (day regimen) or at Months 0, 1, and 6 (month regimen) in participants at US sites. Results from the original planned stage of the study demonstrated that the 200-μg dose level was more immunogenic, as evidenced by numerically higher proportions of participants achieving antibody levels ≥ prespecified thresholds, GMCs, and GMFRs, than the 100-μg dose level in both dosing regimens. The month regimen resulted in numerically higher post-Dose 3 immune response for both the 100-μg and 200-μg dose levels, particularly for toxin B in participants who were seronegative at baseline. The immune responses by age group (65 to 69 years, 70 to 74 years, and 75 to 79 years) were similar to that of the combined age group (65 to 85 years) as determined by proportions of participants achieving both toxin A– and toxin B–specific neutralizing antibody levels ≥ specified thresholds, GMCs, and GMFRs at 1 month after Dose 3 for the month regimen and 7 days after Dose 3 for the day regimen. The number of participants 80 to 85 years of age was small and the interpretation of results for this age group should be conducted with caution. Local reactions increased after Dose 2 for both regimens, but it was to a greater extent when it was administered at Day 8 in the day regimen, particularly at the 200-μg dose level. Rates of systemic events were similar between placebo and the 2 vaccine dose levels. Overall, the AE profile observed in this study identified no untoward safety signals. Overall, the *C difficile* vaccine was highly immunogenic, was well tolerated, and exhibited an acceptable safety profile.

The extension phase of this study is ongoing to assess persistence of neutralizing antibody titers against toxins A and B for up to 4 years after Dose 3.

The ongoing Phase 3 efficacy study (B5091007) is a placebo-controlled, randomized (1:1, vaccine : placebo), observer-blinded, parallel-group study in participants 50 years of age or older who have an increased risk of CDI. In the absence of an accepted immunological correlate of protection for CDI, vaccine efficacy (VE) will be determined by comparing the CDI incidence in recipients of the investigational vaccine with those receiving placebo.

The ongoing Phase 3 lot-consistency study (B5091008) is a placebo-controlled, randomized 1:1:1:1 (Lot 1 : Lot 2 : Lot 3 : placebo), observer-blinded study to evaluate the lot consistency, safety, tolerability, and immunogenicity of the *C difficile* vaccine 200-µg dose level administered at Months 0, 1, and 6 in healthy adults 65 to 85 years of age. This lot-to-lot study is being conducted to fulfill regulatory requirements for product licensure. Since commercial production of this vaccine will involve multiple manufacturing campaigns and multiple lot productions, it is imperative to demonstrate that vaccination from different lots yields similar responses within an acceptable margin.

The present study (B5091019) is a Phase 3, randomized, observer-blinded study to evaluate the immunogenicity, safety, and tolerability of a 3-dose *C difficile* vaccine regimen compared to a 2-dose *C difficile* vaccine regimen in adults 50 years of age and older.

2.3. Benefit/Risk Assessment

C difficile is the main cause of nosocomial infectious diarrhea in industrialized countries.[2,3,4,5,6] It accounts for 20% to 30% of cases of antibiotic-associated diarrhea and is the most commonly recognized cause of infectious diarrhea in healthcare settings.[7] To date, there is no approved vaccine to prevent primary or recurrent CDI. The increasing burden of CDI on patients and on the healthcare system demonstrates that prevention of CDI constitutes a significant unmet medical need.

The B5091001 first-in-human study, which assessed 3 antigen dose levels (50, 100, and 200 µg) administered either alone or in combination with AlOH at Months 0, 1, and 6 to healthy adults 50 to 85 years of age, demonstrated that the *C difficile* vaccine formulations and dose levels administered were generally well tolerated. Local reactions and systemic events were predominantly mild to moderate, and comprised mostly injection site pain, headache, and fatigue. There was little difference in the number of participants reporting AEs between the dose groups and the placebo group or between vaccine formulations.

The B5091009 Phase 2 study, which assessed 2 antigen dose levels (100 and 200 µg) administered in combination with AlOH at Months 0, 1, and 6 or Days 1, 8, and 30 to healthy adults 65 to 85 years of age, demonstrated that both regimens and both dose levels administered were generally well tolerated. Local reactions were predominantly mild to moderate, with injection site pain being the most frequent manifestation. After Dose 2, local reactogenicity was greater when the vaccine was administered at Day 8 compared to Month 1, particularly for the 200-µg dose level. Systemic events were also predominantly mild to moderate and the incidences of individual events were similar between the placebo group, the 100-µg dose group, and the 200-µg dose group. Within each regimen, the overall AE incidence rates were also similar between the placebo, 100-µg, and 200-µg dose groups. For both regimens, SAEs were numerically higher in the 100-µg and 200-µg dose groups than in the placebo group. However, there was no pattern to these events and no safety concern was identified.

Both studied dose levels resulted in substantial neutralizing antitoxin A and B titers, with the immunogenicity profile following 3 doses administered at Months 0, 1, and 6 being preferred. In addition, the 200-µg dose level was more immunogenic than the 100-µg dose level.

Study B5091010, a first-in-Japanese participants study, was a Phase 1, placebo-controlled, randomized, observer-blinded study to assess the safety, tolerability (primary objectives), and immunogenicity (secondary objectives) of 2 antigen dose levels CCI [redacted] in 2 different dosing regimens (Months 0, 1, and 6 [month regimen] or Days 1, 8, and 30 [day regimen]) in healthy Japanese adults, 65 to 85 years of age. The *C difficile* vaccine was well tolerated when administered in the 0-, 1-, and 6-month regimen with no unexpected AEs observed in this regimen, indicating a favorable safety profile in this elderly population of healthy Japanese adults 65 to 85 years of age when administered in the month regimen. There were 3 participants in the day regimen who reported severe local reactions, leading to the triggering of a stopping rule and discontinuation of subsequent enrollment and dosing in the day regimen; these local reactions resolved. The proportion of participants reporting local reactions and systemic events was generally low across all vaccine groups in the month regimen. In both the month and day regimens, most events were of mild to moderate severity. There were no notable differences between the 100- or 200-µg dose groups observed within each regimen based on an evaluation of the proportion of participants reporting AEs, SAEs, or newly diagnosed chronic medical conditions (NDCMCs).

Thus, *C difficile* vaccinations at a dose of 100 or 200 µg were generally well tolerated when given according to a Month 0, 1, and 6 regimen.

Pfizer considers that the available information from Studies B5091001, B5091009, and B5091010 with PF-06425090 supports a favorable benefit-risk profile for studies administrating 3 doses of the *C difficile* vaccine at dose levels up to 200 µg CCI [redacted] as a potential prevention against CDI. It is expected that this would also apply to a 2-dose regimen of the vaccine given 6 months apart, and especially so since the reactogenicity after Dose 2 (at Month 1 seen in all 3 studies, B5091001, B5091009, and B5091010) was the most pronounced. In addition, this is further supported by review of safety data from the B5091007 and B5091008 studies CCI [redacted] which has not identified a safety concern.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of *C difficile* vaccine may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary Immunogenicity:	**Coprimary Immunogenicity:**	**Primary Immunogenicity:**
• To demonstrate the noninferiority of a 2-dose regimen of the *C difficile* vaccine compared to a 3-dose regimen of the *C difficile* vaccine.	• For each of toxin A– and toxin B–specific neutralizing antibody levels: Adjusted GMC ratio, estimated by the ratio of the adjusted GMC (adjusted for baseline concentration) for the 2-dose regimen to the adjusted GMC for the 3-dose regimen, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). • For each of toxin A– and toxin B–specific neutralizing antibody levels: Seroresponse difference, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). Seroresponse for each of toxin A– and toxin B– specific neutralizing antibody levels: For both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from the baseline neutralizing antibody level following vaccination.	• *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 7 in each regimen.
Primary Safety:	**Primary Safety:**	**Primary Safety:**
• To evaluate the safety of *C difficile* vaccine when administered to participants in a 2-dose regimen or a 3-dose regimen by assessing local reactions and systemic events, AEs, and SAEs.	• In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting local reactions. • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of	• Local reactions (pain, erythema, and induration), as self-reported on e-diaries for up to 7 days following each dose of investigational product in each regimen. • Systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint

Objectives	Estimands	Endpoints
	participants reporting systemic events. • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting nonserious AEs. • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting SAEs.	pain), as self-reported on e-diaries for up to 7 days following each dose of investigational product in each regimen. • Nonserious AEs from signing of the ICD to 1 month after receipt of the last dose of investigational product in each regimen. • SAEs from signing of the ICD to 6 months after receipt of the last dose of investigational product in each regimen.
Secondary:	**Secondary:**	**Secondary:**
• To demonstrate the noninferiority of a 2-dose regimen of the *C difficile* vaccine compared to a 3-dose regimen of the *C difficile* vaccine.[a]	• For each of toxin A– and toxin B–specific neutralizing antibody levels: Adjusted GMC ratio, estimated by the ratio of the adjusted GMC (adjusted for baseline concentration) for the 2-dose regimen to the adjusted GMC for the 3-dose regimen, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). • For each of toxin A– and toxin B–specific neutralizing antibody levels: Seroresponse difference, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). Seroresponse for each of toxin A– and toxin B– specific neutralizing antibody levels: For both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from	• *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 12 in each regimen.

Objectives	Estimands	Endpoints
	the baseline neutralizing antibody level following vaccination.	

CCI [redacted]

a. Noninferiority (NI) analysis for Month 12 will be performed only after the NI criteria are met in terms of the GMC ratio and the seroresponse difference at Month 7.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, observer-blinded study to evaluate the immunogenicity, safety, and tolerability of a 2-dose *C difficile* vaccine regimen compared to a 3-dose *C difficile* vaccine regimen in adults 50 years of age and older.

Participants will be randomly assigned in parallel in a 1:1 ratio to receive one of the following dosing regimens according to the visit schedule:

- 2-Dose: Participants will receive 1 dose of *C difficile* vaccine (200 μg total toxoid per dose) at Visit 1 (Month 0) and Visit 4 (Month 6) and 1 dose of placebo (0.9% sodium chloride or normal saline) at Visit 2 (Month 1).

- 3-Dose: Participants will receive 1 dose of *C difficile* vaccine (200 μg total toxoid per dose) at Visit 1 (Month 0), Visit 2 (Month 1), and Visit 4 (Month 6).

4.1.1. Approximate Number of Participants

Approximately 1960 participants will be randomized into the study, with a randomization ratio of 1:1 (2-dose *C difficile* vaccine : 3-dose *C difficile* vaccine).

To achieve a broad representation of age groups among those 50 years of age and older, randomization into an age cohort will be managed by the central randomization process. The targeted number of participants and age cohorts intended to be randomized is shown in Table 1.

Table 1. Intended Numbers of Participants Included in the Study, by Age

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

4.1.2. Approximate Duration of the Study

It is estimated that this study will be completed in approximately 19 months. It is anticipated that recruitment will be completed in approximately 7 months.

4.1.3. Approximate Duration of Participation for Each Participant

Participants will be followed from the time they sign the ICD until 6 months after receipt of their last vaccination. Therefore, individual participants will participate in the study for approximately 12 months.

4.2. Scientific Rationale for Study Design

The mechanism of action (MOA) for prevention of CDI is very well established, both preclinically and clinically, and is based on toxin-neutralizing antibodies.[21,43-49]

Demonstrating that the 2-dose vaccine regimen can generate comparable noninferior antibody responses compared with the 3-dose vaccine regimen provides the clinical rationale for a 2-dose vaccine regimen. This argument may be informed by the successful efficacy anticipated to be demonstrated in the pivotal B5091007 clinical endpoint efficacy study. Efficacy in Study B5091007 may be associated with an immunological profile after the third dose at 6 months in participants who received a 3-dose regimen at Months 0, 1, and 6. Therefore, if participants who received a 2-dose regimen at Months 0 and 6 achieve a noninferior comparable immunological response 1 month after their Month 6 dose compared with the response achieved by the participants who received a 3-dose regimen 1 month after their third dose at Month 6, where efficacy against a clinical endpoint is established, one can infer that similar VEs would be seen with the 2-dose vaccine regimen and the 3-dose vaccine regimen. A similar approach was used in the HPV vaccine program, where efficacy was inferred in adolescents (9 to 15 years of age) based on an immunological profile comparable to the adult female population (16 to 26 years of age), in which efficacy had been established.[1]

4.3. Justification for Dose

Dose selection was derived from Study B5091009 where 2 doses (100 µg and 200 µg) and 2 dosing regimens (Months 0, 1, and 6; and Days 1, 8, and 30) were compared against placebo.

The study demonstrated that the 200-µg dose level was more immunogenic as evidenced by numerically higher proportions of participants achieving antibody levels ≥ threshold, GMCs, and GMFRs than those for the 100-µg dose level in both dosing regimens; and that the month regimen resulted in a higher post–Dose 3 immune response for both the 100-µg and 200-µg dose levels.

Based on these results from Study B5091009, the dosing level to be used in Phase 3 studies is 200 µg, and the regimen to be used is 3 doses administered by intramuscular (IM) injection at Months 0, 1, and 6.

Hence, 200 µg will be used for both the 2-dose regimen (at Months 0 and 6) and the 3-dose regimen (at Months 0, 1, and 6).

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the last scheduled procedure shown in the schedule of activities (SoA).

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

5. STUDY POPULATION

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

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants 50 years of age or older at enrollment.

    - Refer to Appendix 3 for reproductive criteria for male (Section 10.3.1) and female (Section 10.3.2) participants.

Type of Participant and Disease Characteristics:

2. Willing and able to comply with scheduled visits, vaccination plan, and other study procedures.

3. Participants with an increased risk of future contact with healthcare systems by virtue of:

    - At least 1 inpatient hospitalization of ≥2 nights' duration in the previous 12 months; or

    - At least 2 emergency room visits in the previous 12 months; or

    - At least 10 outpatient visits (primary and/or secondary care visits but excluding pharmacy and mental health visits) in the previous 12 months; or

    - Residence in a skilled nursing facility (a residential institution that provides professional nursing care and rehabilitation services, usually following discharge from the hospital); or

    - Residence in a nursing home (a residential institution that provides assistance with activities of daily living); or

    - Inpatient hospitalization of ≥2 nights' duration scheduled ≥37 days after randomization.

Or participants who have received systemic (ie, oral or injected) antibiotics at any time in the previous 12 weeks.

4. Ability to be contacted by telephone during study participation.

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Pregnant female participants; breastfeeding female participants; positive urine pregnancy test for women of childbearing potential (WOCBP); and WOCBP who are, in the opinion of the investigator, sexually active and at risk for pregnancy and are unwilling or unable to use an effective method of contraception as outlined in this protocol from the signing of the informed consent until at least 28 days after the last dose of investigational product.

Medical Conditions:

2. Prior episode of CDI, confirmed by either laboratory test or diagnosis of pseudomembranous colitis at colonoscopy, at surgery, or histopathologically.

3. Participants who may be unable to respond to vaccination due to:

   - Metastatic malignancy; or
   - End-stage renal disease (glomerular filtration rate <15 mL/min/1.73 m2 or on dialysis).
   - Any serious medical disorder that in the investigator's opinion is likely to be fatal within the next 12 months.
   - Congenital or acquired immunodeficiency.

4. Known infection with human immunodeficiency virus (HIV).

5. Any bleeding disorder or anticoagulant therapy that would contraindicate IM injection.

6. Any contraindication to vaccination or vaccine components, including previous anaphylactic reaction to any vaccine or vaccine-related components.

7. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior 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 participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

8. Previous administration of an investigational *C difficile* vaccine or *C difficile* mAb therapy.

9. Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days within 28 days before enrollment.

10. Receipt of chronic systemic treatment with other known immunosuppressant medications, or radiotherapy, within 6 months before enrollment.

11. Receipt of blood products or immunoglobulins within 6 months before enrollment.

Prior/Concurrent Clinical Study Experience:

12. Participation in other studies involving investigational drug(s)/vaccine(s) within 28 days prior to study entry until Visit 5 (1 month after the third vaccination).

Diagnostic Assessments:

Not applicable.

Other Exclusions:

13. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.2.1. Criteria for Temporary Delay of Vaccination

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

1. Current febrile illness (oral temperature of ≥100.4°F [38.0°C]) or other acute illness within 48 hours prior to investigational product administration.

2. Participant has received seasonal or pandemic influenza vaccine within the previous 14 days or any other noninfluenza nonstudy vaccine within the previous 28 days before investigational product administration.

3. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days.
   Inhaled, intra-articular/intrabursal, or topical corticosteroids are permitted.

If a participant 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.

5.3. Lifestyle Considerations

No restrictions are required.

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 3 [Section 10.3.4]) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs recorded from signing the informed consent.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number if they meet eligibility criteria.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

For this study, the investigational products are *C difficile* vaccine and placebo (saline). Since the appearance of these investigational products is not identical, the study is observer blinded.

6.1. Study Intervention(s) Administered

The investigational *C difficile* vaccine (PF-06425090) is toxoid based. *C difficile* toxin A and toxin B are inactivated by a combination of genetic mutations and chemical treatments.

CCI [redacted]

Participants randomized to the 2-dose regimen will receive 2 doses of *C difficile* vaccine (200 µg total toxoid per dose) and 1 dose of placebo (sterile normal saline solution, 0.9% sodium chloride).

Participants randomized to the 3-dose regimen will receive 3 doses of *C difficile* vaccine (200 µg total toxoid per dose).

Please refer to Table 2 below for the description of study intervention(s)s that will be administered.

Table 2. Description of Study Intervention(s)

Intervention Name	PF-06425090	Placebo for PF-06425090
Regimen	*C difficile* vaccine (200 µg) 3-dose regimen and *C difficile* vaccine (200 µg) 2-dose regimen	*C difficile* vaccine (200 µg) 2-dose regimen
Type	Vaccine	Placebo
CCI [redacted]	[redacted]	[redacted]
Unit Dose Strength(s)	200 µg/dose (0.5 mL)	0.9% sodium chloride (0.5 mL)
Dosage Level(s)	0.5-mL dose at Visits 1, 2, and 4 (Months 0, 1, and 6) for 3-dose regimen 0.5-mL dose at Visits 1 and 4 (Months 0 and 6) for 2-dose regimen	0.5-mL dose at Visit 2 (Month 1) for 2-dose regimen only
Route of Administration	Intramuscular	Intramuscular
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP	IMP

CCI

[redacted]

The investigational products will be provided by the sponsor to each study site. Investigational product and diluent will be packed and labeled by Pfizer or its designee as investigational product in accordance with current guidelines and applicable local and legal regulatory requirements. For detailed information on the antigenic components of the investigational product, please refer to the IB.

6.1.1. Administration

All injections will be administered in the upper deltoid muscle, preferably of the nondominant arm, by the unblinded administrator.

Participants will be administered the following injections according to the dosing regimen to which the participant is randomized:

- 2-Dose: Participants will receive 1 dose of C difficile vaccine (200 µg total toxoid per dose) at Visit 1 (Month 0) and Visit 4 (Month 6) as well as 1 dose of placebo (0.9% sodium chloride or normal saline) at Visit 2 (Month 1).

- 3-Dose: Participants will receive 1 dose of C difficile vaccine (200 µg total toxoid per dose) at Visit 1 (Month 0), Visit 2 (Month 1), and Visit 4 (Month 6).

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 immunization practices.

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, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Investigational product administration details will be recorded on the case report form (CRF).

6.1.2. Medical Devices

In this study, medical devices being deployed will be vial adapter and PFS for *C difficile* vaccine and PFS only for placebo (0.9% sodium chloride or normal saline).

Instructions for medical device use are provided in the IP manual.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the unblinded study personnel throughout the study. Please refer to Section 8.3.6 for details.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

CCI [redacted]

3. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

5. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

6. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

7. Study interventions should be stored in their original containers and in accordance with the labels.

8. See the IP manual for storage conditions of the study intervention once reconstituted.

9. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

10. Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

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

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and administered by an appropriately qualified and experienced **unblinded** member of the study staff.

6.3. Measures to Minimize Bias: Randomization and Blinding

For this study, the investigational products are *C difficile* vaccine and placebo (saline). Since the appearance of these investigational products is not identical, the study is observer blinded. The study staff dispensing and administering the vaccine will be unblinded, but all other site study personnel, including the principal investigator and the participant, will be blinded.

6.3.1. Allocation to Investigational Product

Allocation of participants to vaccine groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]) in a randomization ratio of 1:1. Study personnel (either blinded or unblinded) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. They will then be provided with a randomization number, and dispensable unit (DU) or container number. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be retained by the unblinded dispenser in the unblinded site files.

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

6.3.2. Blinding of Site Personnel

The principal investigator will assign the responsibility of the unblinded dispenser/administrator to persons who will not participate in the evaluation of any study participant. More than 1 unblinded dispenser/administrator may be assigned per site. Members of the study site staff or clinic pharmacy should fulfill this role. Contact between the unblinded dispenser and study participants 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 participant and must not be allowed to see the investigational product container contents.

6.3.3. 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 (eg, study manager; clinical research associates [CRAs]; and unblinded clinician) will be unblinded for the duration of the study. Sponsor study team members will remain blinded until the snapshot for the interim analysis is taken (once all participants have completed Visit 5 [Month 7]) and will be unblinded thereafter [see Section 9.5]. Laboratory personnel performing the serology assays will remain blinded to vaccine assigned/received throughout the study.

6.3.4. Breaking the Blind

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual vaccine assignment is absolutely essential for further management of the participant. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

6.4. Study Intervention Compliance

All doses of investigational product will be administered by the appropriately designated unblinded study staff at the investigator site.

6.5. Concomitant Therapy

6.5.1. Recording Concomitant Vaccinations and Medications

The following concomitant medications and vaccinations will be recorded in the CRF. All vaccinations received from 28 days prior to study enrollment until Visit 5 (Month 7 [1 month after the third vaccination]).

6.5.2. Prohibited Concomitant Vaccinations and Medications

Receipt of the following prohibited vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see Section 7.2).

Unless considered medically necessary, no vaccines other than investigational product should be administered within 28 days before and 28 days after each study vaccination (administered at Visits 1, 2, and 4). Exceptions to this are the seasonal influenza vaccine and pandemic influenza vaccine, which can be given at least 14 days prior to or 14 days after the administration of investigational product.

- Receipt of chronic systemic treatment with other known immunosuppressant medications, or radiotherapy, within 6 months before enrollment through conclusion of the study.

- Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment to Visit 5 (Month 7).

- Receipt of blood products or immunoglobulins within 6 months before enrollment through conclusion of the study.

- Receipt of any other (nonstudy) investigational *C difficile* vaccine or *C difficile* mAb therapy at any time prior to or during study participation is prohibited.

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

6.5.3. 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 6.5.2 required for treatment of preexisting stable conditions is permitted.

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

- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 3).

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participant eligibility must be confirmed prior to each vaccination in order to continue in the study.

If a participant no longer meets the eligibility criteria during the vaccination period of the study, discontinuation of further vaccinations should be considered, but the participant may remain in the study. If a participant is discontinued from vaccination and the participant consents, safety follow-up will be conducted as per Section 8.3.1 (AEs will be collected for 1 month after the last dose of investigational product and SAEs will be collected for 6 months after the last dose of investigational product).

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing, please refer to the study reference manual (SRM) and SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

If the participant withdraws from the study and also withdraws consent (see below) 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.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant.

When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

Visit 1: Month 0 – Vaccination 1

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Obtain written informed consent prior to performing any protocol-required procedures.
- Record the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Conduct a clinical assessment, including review of medical history, to verify that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria (Section 5.2.1) are met. Record medical history of significance, including the presence of chronic medical conditions. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record the findings.
- Record nonstudy vaccines as described in Section 6.5.
- Measure and record the participant's weight and height.
- Measure and record the participant's oral temperature.
- For WOCBP, perform a urine pregnancy test and ensure the result is negative prior to vaccination (Section 8.2.4).
- Discuss contraceptive use.
- An appropriate site staff member (may be blinded or unblinded) will use the IRT system to obtain the participant's randomization number and DU or container number.
- Collect a blood sample of approximately 20 mL for immunogenicity testing (Section 8.1.1).

- Unblinded site staff will prepare and administer investigational product. Investigational product will be administered by IM injection into the upper deltoid muscle, preferably of the nondominant arm. The time of vaccination will be recorded. Refer to the IP manual under separate cover for further instruction on this process.

- The unblinded vaccine dispenser/administrator updates the investigational product accountability records.

- Blinded study staff will observe the participant for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded in the CRF.

- Record and report AEs and SAEs (relative to the time of vaccination) as described in Section 8.3 and the SoA.

- Issue a measuring device for measurement of local reactions, and a digital thermometer for recording daily temperatures. Provide instructions on their use and recording.

- Explain the e-diary platform to collect vaccine reactogenicity data and provide instructions on its completion. Ask the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Schedule an appointment for the participant to return for the next study visit.

- Complete the source documents.

- Complete the CRF.

Visit 2: Month 1 –Vaccination 2 (28 to 42 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Review the participant's e-diary data and follow up on any ongoing local reactions or systemic events.

- Ensure that the participant continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 7.2.

- 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 8.3 and the SoA. Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.

- Record nonstudy vaccines as described in Section 6.5.

- Measure and record the participant's oral temperature.

- For WOCBP, perform a urine pregnancy test and ensure the result is negative prior to vaccination (Section 8.2.4).

- Discuss contraceptive use.

- Ensure that none of the temporary delay criteria are met (Section 5.2.1).

- An appropriate site staff member (may be blinded or unblinded) will use the IRT system to obtain the participant's investigational product blinded carton number.

- Unblinded site staff will prepare and administer investigational product. Investigational product will be administered by IM injection into the upper deltoid muscle, preferably of the nondominant arm. The time of vaccination will be recorded. Refer to the IP manual under separate cover for further instruction on this process.

- The unblinded vaccine dispenser/administrator updates the investigational product accountability records.

- Blinded study staff will observe the participant for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded in the CRF.

- Record and report AEs and SAEs (relative to the time of vaccination) as described in Section 8.3 and the SoA.

- Ensure the participant has an available measuring device for measurement of local reactions, and a digital thermometer for recording daily temperatures. If required, provide instructions on their use.

- Confirm that the participant understands the reactogenicity reporting requirements. Remind the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.

- Schedule a telephone call for the next study visit.
- Complete the source documents.
- Complete the CRF.

Visit 3: Month 2 - Telephone Contact (28 to 42 Days After Visit 2)

- Contact the participant by telephone to determine whether any AEs or SAEs have occurred since the last study visit. Record and report findings as described in Section 8.3 and the SoA. Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Follow up on any ongoing local reactions or systemic events.
- Record nonstudy vaccines as described in Section 6.5.
- Discuss contraceptive use.
- Ensure that the participant continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 7.2.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

Visit 4: Month 6 -Vaccination 3 (140 to 168 Days After Visit 2)

- Review the participant's e-diary data and follow up on any ongoing local reactions or systemic events.
- Ensure that the participant continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 7.2.
- 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 8.3 and the SoA. Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines as described in Section 6.5.

- Collect a blood sample of approximately 20 mL for immunogenicity testing (Section 8.1.1).
- Measure and record the participant's oral temperature.
- For WOCBP, perform a urine pregnancy test and ensure the result is negative prior to vaccination (Section 8.2.4).
- Discuss contraceptive use.
- Ensure that none of the temporary delay criteria are met (Section 5.2.1).
- An appropriate site staff member (may be blinded or unblinded) will use the IRT system to obtain the participant's investigational product blinded carton number.
- Unblinded site staff will prepare and administer investigational product. Investigational product will be administered by IM injection into the upper deltoid muscle, preferably of the nondominant arm. The time of vaccination will be recorded. Refer to the IP manual under separate cover for further instruction on this process.
- The unblinded vaccine dispenser/administrator updates the investigational product accountability records.
- Blinded study staff will observe the participant for at least 30 minutes after investigational product administration for any acute reactions. Any AEs noted during the observation period should be recorded in the CRF.
- Record and report AEs and SAEs (relative to the time of vaccination) as described in Section 8.3 and the SoA.
- Ensure the participant has an available measuring device for measurement of local reactions, and a digital thermometer for recording daily temperatures. If required, provide instructions on their use.
- Confirm that the participant understands the reactogenicity reporting requirements. Remind the participant to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

- Complete the CRF.

Visit 5: Month 7 (28 to 42 Days After Visit 4)

- Review the participant's e-diary data and follow up on any ongoing local reactions or systemic events.
- Collect the participant's e-diary.
- Ensure that the participant continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 7.2.
- 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 8.3 and the SoA. Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines as described in Section 6.5.
- Collect a blood sample of approximately 20 mL for immunogenicity testing (Section 8.1.1).
- Collect an additional (optional) blood sample of approximately 40 mL for the purposes of vaccine assay development.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- Complete the CRF.

Visit 6: Month 9 (84 to 98 Days After Visit 4)

- Ensure that the participant continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 7.2.
- Based on clinical evaluation, determine whether any SAEs have occurred since the last study visit. Record and report findings as described in Section 8.3 and the SoA. Review 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 8.1.1).

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

Visit 7: Month 12 (165 to 195 Days After Visit 4)

- Based on clinical evaluation, determine whether any SAEs have occurred since the last study visit. Record and report findings as described in Section 8.3 and the SoA. Review 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 8.1.1).

Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 8.2.1.2), systemic event (Section 8.2.1.3), or fever (Section 8.2.1.4) is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated.

If a suspected Grade 4 local reaction (Section 8.2.1.2), systemic event (Section 8.2.1.3), or fever (Section 8.2.1.4) is reported, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the investigational product, further vaccinations will be discontinued in that participant. The Grade 4 reaction must be recorded in the CRF and is not collected in the e-diary.

8.1. Efficacy Assessments

Not applicable.

8.1.1. Immunogencity Assessments

Both toxin A– and toxin B–specific neutralizing antibody levels will be measured. Approximately 20 mL (minimum of 10 mL and up to 20 mL) of blood will be collected (at Visit 1, Visit 4 [these must be prior to vaccination], Visit 5, Visit 6, and Visit 7) for each measurement to allow for adequate volume required for repeat testing or additional antigen-specific immunogenicity testing to be performed.

An additional (optional) 40 mL of blood at Visit 5 will be taken for the purposes of vaccine assay development.

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

8.2. Safety Assessments

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

A clinical assessment, including medical history, will be performed on all participants at Visit 1 to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in Section 8.3.

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

The safety parameters also include e-diary reports of local reactions and systemic events that occur in the 7 days after investigational product administration. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 8.2.1.

8.2.1. Electronic Diary

Participants will be required to use an e-diary, based on appropriate technology, and will be asked to monitor and record local reactions and systemic events for 7 days following investigational product administration. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported on the e-diary will be transferred electronically to a third-party 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 participant e-diary data-entry periods (7 days after each vaccination).

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 as AEs.

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 obtain stop dates for any ongoing local reactions or systemic events 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.

8.2.1.1. 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.[56]

8.2.1.2. Local Reactions

During the e-diary reporting period, participants 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 participant will be requested to report that information. 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 3. 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 participant as absent, mild, moderate, or severe according the grading scale in Table 3.

If a Grade 3 local reaction is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the investigational product, further vaccinations will be discontinued in that participant. The Grade 4 reaction must be recorded in the CRF and is not collected in the e-diary.

Table 3. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Erythema/Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Induration/Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

8.2.1.3. Systemic Events

During the e-diary reporting period, participants will be asked to assess vomiting, 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 participant as absent, mild, moderate, or severe according to the grading scale in Table 4.

If a Grade 3 systemic event is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the investigational product, further vaccinations will be discontinued in that participant. The Grade 4 reaction must be recorded in the CRF and is not collected in the e-diary.

Table 4. Systemic Event Grading Scale

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

Abbreviation: IV = intravenous.

8.2.1.4. Fever

In order to record information on fever, a digital thermometer will be given to participants 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. Fever is defined as an oral temperature of ≥38.0°C (100.4°F). The highest temperature for each day will be recorded in the e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 5.

If a Grade 3 fever is reported in the e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's fever as Grade 4. If a participant experiences a confirmed Grade 4 fever, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the investigational product, further vaccinations will be discontinued in that participant. The Grade 4 reaction must be recorded in the CRF and is not collected in the e-diary.

Table 5. Scale for Fever

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

8.2.2. Clinical Safety Laboratory Assessments

Clinical safety laboratory tests will not be performed in this study.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.3. Biological Samples

Serum samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed.

8.2.4. Pregnancy Testing

Urine pregnancy tests must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA, immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the investigational product. Pregnancy tests may also be repeated if

requested by IRBs/ ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of investigational product and from the study.

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE or that caused the participant to discontinue the study (see Section 7).

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

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including Visit 5 (Month 7) for AEs and through and including Visit 7 (Month 12) for SAEs.

In addition, any AE occurring up to 48 hours after each blood draw (ie, after Visits 6 [Month 9] and 7 [Month 12]) must be recorded on the CRF.

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

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

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until Visit 7 (Month 12).

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. 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 Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the

information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of administering investigational product. In order to fulfill regulatory reporting obligations worldwide, the unblinded site staff are responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a medical device incident can be found in Appendix 5.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.6.1. Time Period for Detecting Medical Device Incidents

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

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

The method of documenting medical device incidents is provided in Appendix 5.

8.3.6.2. Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3). This applies to all participants, including those who discontinue study intervention.

The unblinded site staff are responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the unblinded site staff.

8.3.6.3. Prompt Reporting of Medical Device Incidents to Sponsor

Medical device incidents will be reported to the sponsor within 24 hours after unblinded site staff determines that the event meets the protocol definition of a medical device incident.

The Medical Device Incident Report Form will be sent to the sponsor by an electronic method. If an electronic method is unavailable, then an alternative method should be utilized.

The same individual will be the contact for the receipt of medical device reports and SAEs.

8.3.6.4. Regulatory Reporting Requirements for Medical Device Incidents

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

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

8.3.7. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant 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 study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

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

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

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.

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than 1 dose of investigational product within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose. In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

The primary objective of assessing noninferiority of the 2-dose regimen to the 3-dose regimen will be evaluated at 1 month after the last vaccination for each *C difficile* toxin A– or toxin B–specific neutralizing antibody. The evaluable immunogenicity population will be used for the hypothesis testing to assess the primary immunogenicity objective.

The 2 null hypotheses (H_0) for noninferiority are:

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

Where, for each of toxin A– and toxin B–specific neutralizing antibody, $\ln(\mu_2)$ and $\ln(\mu_3)$ are the means of the natural logarithm-transformed concentrations from participants receiving the 2-dose regimen and the 3-dose regimen, respectively, measured 1 month after the last vaccination with the *C difficile* vaccine (Month 7). The analysis of covariance (adjusted for baseline concentration) will be used to test these null hypotheses, and corresponding 95% CIs will be provided.

and

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

Where, for each of toxin A– and toxin B–specific neutralizing antibody, P_2 and P_3 are the seroresponse rates achieved by participants receiving the 2-dose regimen and the 3-dose regimen respectively, measured 1 month after the last vaccination with *C difficile* vaccine (Month 7). A participant achieves seroresponse if the participant has a 4-fold rise after vaccination.

If the lower limit of the 2-sided 95% CI for the GMC ratio (2-dose/3-dose) is > 0.67 and the lower limit of the 2-sided 95% CI for the difference between the regimens (2-dose minus 3-dose) in the percentage of participants achieving seroresponse is > -10% for both toxin A– and toxin B–specific neutralizing antibodies, 1 month after the last vaccination, the primary objective of establishing noninferiority of the 2-dose regimen to the 3-dose regimen is met.

If this primary immunogenicity objective is met, the same null hypotheses for the secondary immunogenicity objective will be evaluated 6 months after the last vaccination.

Estimands

Endpoint	Estimands

Primary	• Immunogenicity:
	
	For each of toxin A– and toxin B–specific neutralizing antibody levels: Adjusted GMC ratio, estimated by the ratio of the adjusted GMC at Month 7 (adjusted for baseline concentration), for the 2-dose regimen to the adjusted GMC for the 3-dose regimen, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants).
	
	For each of toxin A– and toxin B–specific neutralizing antibody levels: Seroresponse difference at Month 7, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants).
	
	Seroresponse for each of toxin A– and toxin B– specific neutralizing antibody levels: For both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from the baseline neutralizing antibody level following vaccination.
	
	These estimands estimate the regimen effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. They address the primary immunogenicity objective of estimating the (maximum) potential difference between the 2- and 3-dose regimens at 1 month post last vaccination, since the impact of noncompliance may diminish the observed difference between the 2 regimens (eg, when participants randomized to the 3-dose regimen receive only 2 doses). Missing serology results will not be imputed, as missing completely at random (MCAR) is assumed.
	
	• Safety:
	  • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting local reactions.
	
	  • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting systemic events.
	
	  • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting nonserious AEs.
	
	  • In participants receiving at least 1 dose of investigational product, the incidence rate estimated by the percentage of participants reporting SAEs.
	
	Missing e-diary data will not be imputed; missing AE dates and missing AE severity will be handled according to the Safety Rulebook Summary developed by Pfizer.

Endpoint	Estimands
Secondary	For each of toxin A– and toxin B–specific neutralizing antibody levels: Adjusted GMC ratio, estimated by the ratio of the adjusted GMC at Month 12 (adjusted for baseline concentration), for the 2-dose regimen to the adjusted GMC for the 3-dose regimen, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). For each of toxin A– and toxin B–specific neutralizing antibody levels: Seroresponse difference at Month 12, estimated by the difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse, in participants receiving *C difficile* vaccine and in compliance with the key protocol criteria (evaluable participants). Seroresponse for each of toxin A– and toxin B– specific neutralizing antibody levels: For both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is achieved for a specific participant if that participant has at least a 4-fold rise from baseline neutralizing antibody level following vaccination. These estimands estimate the regimen effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. They address the secondary objective of estimating the (maximum) potential difference between the 2- and 3-dose regimens at 6 months post last vaccination, since the impact of noncompliance may diminish the observed difference between the 2 regimens (eg, when participants randomized to the 3-dose regimen receive only 2 doses). Missing serology results will not be imputed, as MCAR is assumed.

9.2. Sample Size Determination

In order to meet the immunogenicity primary objective, the study sample size estimate is based upon the evaluation of the primary immunogenicity objective of the study to demonstrate that the immune responses induced by 2 doses of *C difficile* vaccine (administered in a 0- and 6-month regimen) are noninferior to the immune responses induced by 3 doses of *C difficile* vaccine (administered in a 0-, 1-, and 6-month regimen) – by evaluating the toxin A- and toxin B- specific neutralizing antibody in terms of GMC ratios and difference in the percentage of participants achieving seroresponse, 1 month after the last investigational product administration. Regimen comparisons will be based on two primary endpoints: (1) the adjusted GMC ratio (adjusted for baseline antibody concentration); and (2) the difference in the percentage of participants achieving seroresponse, 1 month after the last vaccination (Month 7), and the corresponding 95% CIs. The noninferiority of a 2-dose regimen to a 3-dose regimen at 1 month after the last vaccine dose will be evaluated using a 1.5-fold NI margin for the adjusted GMC ratio and a 10% NI margin for the difference in seroresponse rates. Pfizer has developed a new assay which will be used for serology testing in this study. The new assay was used to test Study B5091009 retrospectively, and the standard deviation was evaluated. Therefore, the computation of the sample size for the GMC ratio is based on (1) the standard deviations (0.794 for toxin A and 1.059 for toxin B) from Study B5091009 data tested by the new assay and (2) an assumption that the true mean difference between the 2 regimens for both toxin A– and toxin B–specific neutralizing antibody levels is no more than 0.2 on the logarithmic scale. Similarly, the reference for the computation of the sample size for the difference in seroresponse rate is based on the percentage of seroresponse (4-fold rise from baseline) observed from Study B5091009, and an assumption that the true seroresponse rate for the 2-dose regimen is no more than 7% lower than the ones from the 3-dose regimen. A sample size of 784 evaluable participants per regimen will provide a power of 96.91% to declare the noninferiority of a 2-dose regimen to a 3-dose regimen for both toxin A and toxin B in terms of the GMC ratio, 1 month after the last dose (see Table 6). The sample size will also provide a power of 93.43% to declare the noninferiority of a 2-dose regimen to a 3-dose regimen for both toxin A and toxin B in terms of the difference of percentage of participants achieving seroresponse, 1 month after the last dose (see Table 7). Thus, the overall power to meet the study primary immunogenicity objective is 90.5%.

Table 6. Power Analysis (Primary Immunogenicity Objective: Noninferiority for GMC ratio)

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

Abbreviations: GMC = geometric mean concentration; NI = noninferiority.
a. Reference Study B5091009 tested by new assay, 1 month after Dose 3.
b. At 0.05 alpha level (2-sided).

Table 7. Power Analysis (Primary Immunogenicity Objective: Noninferiority for Difference in Seroresponse)

Criteria	Neutralizing Antibody	Observed % of seroresponse from 3-dose group[a]	Assume % of seroresponse from 2-dose group	Number of Evaluable Participants per Regimen	Power[b]	Power to Meet NI for Both Toxins at 1 Month After Dose 3
Lower limit of 95% CI for difference in seroresponse rate (2 doses minus 3 doses) > -10%	Toxin A	91.8%	86%	784	96.14%	93.43%
	Toxin B	93.7%	86%	784	97.18%	

Note: Seroresponse = Participant achieves at least a 4-fold rise after the last vaccination
a. Reference Study B5091009.
b. At 0.05 alpha level (2-sided).

If the primary immunogenicity objective is met, the secondary immunogenicity objective will be evaluated by the same criteria. For the secondary immunogenicity objective, if the noninferiority criterion for the GMC ratio is met at Month 12, then the evaluation of the difference between regimens in seroresponse at Month 12 will follow.

A sufficient number of participants will be screened to achieve 1960 participants randomly assigned to investigational product and 1568 evaluable participants (assuming a maximum study nonevaluable rate of 20% and a randomization ratio of 1:1), for an estimated total of 784 evaluable participants per vaccine group in order to meet the primary immunogenicity objectives.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants who are assigned a randomization number in the IWR system.
Evaluable	All participants who are eligible, have received the investigational product to which they were randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for either toxin A or toxin B for the proposed analysis time point, and have no major protocol violations. For participants who have major protocol violations (eg, took concomitant medications/vaccines that may impact the immune response), all postviolation observations will be censored. Participants who discontinue the study before reaching primary endpoint will be excluded from the primary analysis.
Modified intent-to-treat (mITT)	All participants who are randomly assigned to investigational product and have received at least 1 vaccination and have at least 1 valid and determinate assay result for the proposed analysis. Participants who discontinue the study before reaching the primary endpoint will be excluded from the analysis.
Safety	All participants who are randomly assigned to investigational product and have received at least 1 dose of investigational product. For reactogenicity, it includes all participants who receive the dose and have the e-diary collected; an indicator variable for an e-diary completion status after each dose will be detailed in the SAP. For safety, it includes all participants who receive at least 1 dose. Standard algorithms for handling missing AE dates and missing AE severity will be applied following the Safety Rulebook Summary developed by Pfizer.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Immunogenicity Analyses

Endpoint	Statistical Analysis Methods
Primary	Adjusted GMC ratio of the 2-dose regimen to the 3-dose regimen for each of *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 7 will be computed using an analysis of covariance (adjusted for baseline antibody concentration); corresponding 95% CIs will be provided. The GMC will be calculated as the mean of the assay results after making the logarithm transformation and then transforming the value back to its original scale. Two (2) sided 95% CIs will be obtained by constructing a CI for the mean of the logarithmically transformed assay results based on the Student t distribution, and transforming the confidence limits back to the original units. The difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse will be computed, along with 95% CIs, for each of the *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 7. For each of the toxin A- and toxin B-specific neutralizing antibody levels, for both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is defined as at least a 4-fold rise from the baseline neutralizing antibody following vaccination. Two (2) sided 95% CIs will be constructed by the Miettinen and Nurminen method. Baseline concentration is defined as the antibody concentration results from the blood drawn before vaccine Dose 1. Antibody concentration values below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. This analysis is based on the evaluable population in order to provide a comparison of the 2 regimens that has the greatest chance of identifying a difference between the regimens with respect to immunogenicity, if a meaningful difference actually exists (ie, results of the regimen comparisons fail to establish noninferiority). A secondary analysis will be performed based on the mITT population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.
Secondary	The secondary immunogenicity objective will be evaluated only after the primary immunogenicity objective is met. Adjusted GMC ratio of the 2-dose regimen to the 3-dose regimen for each of *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 12 will be computed using an analysis of covariance (adjusted for baseline antibody concentration); corresponding 95% CIs will be provided. The GMC will be calculated as the mean of the assay results after making the logarithm transformation and then transforming the value back to its original scale. Two (2) sided 95% CIs will be obtained by constructing a CI for the mean of the logarithmically transformed assay results based on the Student t distribution, and transforming the confidence limits back to the original units. The difference between the 2-dose regimen and the 3-dose regimen in the percentage of participants achieving seroresponse will be computed, along with 95% CIs, for each of *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at Month 12. For each of toxin A- and toxin B-specific neutralizing antibody levels, for both seronegative (baseline concentration < LLOQ) and seropositive (baseline concentration ≥ LLOQ) participants, seroresponse is defined as at least a 4-fold rise from the baseline neutralizing antibody following vaccination. Two (2) sided 95% CIs will be constructed by the Miettinen and Nurminen method. Antibody concentration values below the LLOQ or denoted as BLQ will be set to 0.5 × LLOQ for analysis. This analysis is based on the evaluable population in order to provide a comparison of the 2 regimens that has the greatest chance of identifying a difference between the regimens with respect to immunogenicity, if a meaningful difference actually exists (ie, results of the regimen comparisons fail to establish noninferiority). A secondary analysis will be performed based on the mITT population. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.

Endpoint	Statistical Analysis Methods
CCI	[redacted]

9.4.1.1. Analysis of the Primary Immunogenicity Endpoint

For immunogenicity analysis, the evaluable immunogenicity population and the mITT population will be used for the analysis. Participants will be included in the vaccine group according to their randomization at Dose 1. The primary objective will be evaluated by an analysis of covariance to compute the GMC ratio, adjusted for baseline antibody concentration, of the 2-dose regimen to the 3-dose regimen at 1 month after the last dose for each *C difficile* toxin A– and toxin B–specific neutralizing antibody; and by the difference between the regimens in the percentage of participants achieving seroresponse at 1 month after the last dose for each *C difficile* toxin A– and toxin B–specific neutralizing antibody.

If the lower limit of 2-sided 95% CI for the GMC ratio (2-dose/3-dose regimen) is > 0.67 for both toxin A– and toxin B–specific neutralizing antibody concentrations, and the lower limit of the 2-sided 95% CI for the difference in the percentage of participants achieving seroresponse (2-dose minus 3-dose regimen) is > -10% for both toxin A– and toxin B–specific neutralizing antibodies, 1 month after the last vaccination, the primary objective of establishing noninferiority of the 2-dose regimen to the 3-dose regimen is met.

9.4.1.2. Analysis of the Secondary Immunogenicity Endpoints

If the primary objective is met, the secondary immunogenicity objective will be evaluated by the GMC ratio first and then by the difference in percentage of participants achieving seroresponse at 6 months after the last vaccination for each *C difficile* toxin A–and toxin B–specific neutralizing antibody, based on the evaluable immunogenicity population and the mITT population.

If the lower limit of the 2-sided 95% CI for the GMT ratio (2-dose/3-dose regimen) is > 0.67 at Month 12 for both toxin A– or toxin B–specific neutralizing antibody concentrations, and the lower limit of the 2-sided 95% CI for the difference in the percentage of participants achieving seroresponse (2-dose minus 3-dose regimen) is > -10% at Month 12 for both toxin A– and toxin B–specific neutralizing antibody levels, the secondary immunogenicity objective of noninferiority of the 2-dose regimen to the 3-dose regimen 6 months after the last dose is met.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	• The point estimate and the exact 2-sided 95% CI will be calculated using the Clopper-Pearson method for the percentage of participants reporting each event for each vaccine group. • A 3-tier approach will be used to summarize AEs. For both tier 1 and tier 2 events, the 95% CIs for the difference between the 2-dose regimen group and the 3-dose regimen group in the percentage of participants reporting the events, will be calculated using the test statistic proposed by Miettinen and Nurminen; in addition, for tier 1 events, the asymptotic p-values will also be presented for the difference in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed. The safety analyses are based on safety population. Participants will be summarized according to the vaccine they actually received. Missing e-diary data will not be imputed; missing AE dates and missing AE severity will be handled according to the Safety Rulebook Summary developed by Pfizer.
Secondary	• N/A
CCI [redacted]	[redacted]

9.4.2.1. Analysis of the Primary Safety Endpoints

For safety analysis, the safety population will be used, and participants will be analyzed according to the investigational product received. A descriptive summary will be presented for each vaccine group.

The proportions of participants reporting local reactions at the injection site (pain, erythema, and induration), and systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain) on any day within the 7-day period after vaccination will be descriptively summarized by vaccine group and by each vaccination. Severities of local reactions and systemic events reported after each vaccination will also be descriptively summarized by vaccine group. Exact 2-sided 95% CIs will be presented with the proportions.

AEs and SAEs will be categorized according to Medical Dictionary for Regulatory Activities (MedDRA) terms. AEs will be summarized by vaccine group from the signing of the ICD to 1 month after receipt of the third dose of investigational product. SAEs will be summarized by vaccine group from the signing of the ICD to 6 months after receipt of the third dose of investigational product, and throughout the entire study. In general, all summaries will present the number and percentage of participants experiencing at least 1 event and the number of events for each vaccine group, and the exact 2-sided 95% CIs.

CCI

[redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

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

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

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

www.clinicaltrials.gov

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

PCD is defined as the date that the final participant 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.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents Within Marketing Authorization Packages/Submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response

submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the SRM.

10.1.7. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to

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

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.9. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available.

It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

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

10.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.2.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	None	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

10.3.1. Male Participant Reproductive Inclusion Criteria

In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.3.4).

10.3.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.3.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.3.3. Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

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

10.3.4. Contraception Methods

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

2. Intrauterine device (IUD).

3. Hormone-releasing intrauterine system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

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

    - oral;
    - intravaginal;
    - transdermal;
    - injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

    - Oral;
    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Collection of Pregnancy Information

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

- 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).

- 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 participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT 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 participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety 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 Safety 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 to Pfizer Safety 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 sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities**.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.5. Appendix 5: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions of a Medical Device Incident

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

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.

It is sufficient that:

- An **incident** associated with a device happened.

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness;
- Permanent impairment of body function or permanent damage to body structure;
- Condition necessitating medical or surgical intervention to prevent one of the above;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study intervention is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documentation
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 2. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

10.6. Appendix 6: Abbreviations

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

Abbreviation	Term
AE	adverse event
AIOH	aluminium hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the level of quantitation
CBER	Center for Biologics Evaluation and Research
CDI	*Clostridium difficile* infection
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
CCI [redacted]	[redacted]
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
CCI [redacted]	[redacted]
EDP	exposure during pregnancy
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
H_0	null hypothesis

Abbreviation	Term
HPV	human papillomavirus
HRT	hormone replacement therapy
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IDSA	Infectious Diseases Society of America
IgG	immunoglobulin G
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	hormone-releasing intrauterine system
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MOA	mechanism of action
N/A	not applicable
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
PCD	primary completion date
PFGE	pulsed-field gel electrophoresis
PFS	prefilled syringe
PT	prothrombin time
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SRM	study reference manual
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
TBili	total bilirubin
TcdA	*Clostridium difficile* toxin A
TcdB	*Clostridium difficile* toxin B
ULN	upper limit of normal
US	United States
VE	vaccine efficacy
WOCBP	woman/women of childbearing potential

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