A PHASE 3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLINDED STUDY TO EVALUATE THE LOT CONSISTENCY, SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF A *CLOSTRIDIUM DIFFICILE* VACCINE IN HEALTHY ADULTS 65 TO 85 YEARS OF AGE

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:	Not Applicable (N/A)
Protocol Number:	B5091008
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Protocol Amendment 1	08 Nov 2018	*Clostridium difficile* Disease Background, Section 1.2.1, has been updated to reflect the most recent therapy recommendations for the treatment of *Clostridium difficile* infection (CDI), and a reference was added. The secondary endpoints such as geometric mean fold rises (GMFRs) for neutralizing antibody were not intended to explore any additional aspects of the vaccine lot comparisons beyond those assessed for the primary objective. Therefore, the secondary objectives and endpoints were changed to exploratory objectives and endpoints in Sections 2 and 9.2.3. To ensure that subjects continue to meet eligibility requirements at Visit 5, the Schedule of Activities and Procedures (Section 6.1.5) were updated. Medical Device Complaint Reporting Requirements, Section 8.5, has been updated to incorporate the Protocol Administrative Change Letter (PACL), dated 18 April 2018, that prevents accidental unblinding.
Original protocol	08 Jan 2018	N/A

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

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PROTOCOL SUMMARY

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 and Endpoints

Primary Immunogenicity Objective:	**Primary Immunogenicity Endpoint:**
• To demonstrate that the immune responses induced by 3 lots of *C difficile* vaccine are equivalent as measured by *C difficile* toxin A– and toxin B–specific neutralizing antibody levels 1 month after the third vaccination when administered in a 3-dose regimen to healthy adults 65 to 85 years of age.	• *C difficile* toxin A– and toxin B–specific neutralizing antibody levels for each lot, expressed as geometric mean concentrations (GMCs) (neutralization units/mL) at Month 7.
Primary Safety Objective:	**Primary Safety Endpoints:**
• To evaluate the safety of *C difficile* vaccine when administered in a 3-dose regimen to healthy adults 65 to 85 years of age, as measured by the number and percentage of subjects reporting local reactions and systemic events, adverse events, and serious adverse events.	• Local reactions (pain, erythema, and induration), as self-reported in electronic diaries (e-diaries) for up to 7 days following each dose of investigational product. • Systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain), as self-reported in e-diaries for up to 7 days following each dose of investigational product. • Nonserious adverse events from signing of the informed consent document (ICD) to 1 month after receipt of the third dose of investigational product. • Serious adverse events from signing of the ICD to 1 month after receipt of the third dose of investigational product.

Study Design

This is a Phase 3, placebo-controlled, randomized, observer-blinded study to evaluate the lot consistency, safety, tolerability, and immunogenicity of an aluminum hydroxide (AlOH)-containing *C difficile* vaccine (200 μg total toxoid) administered as a 3-dose regimen at Months 0, 1, and 6 in healthy adults 65 to 85 years of age.

Subjects will be randomized into 1 of 4 groups in a 1:1:1:1 ratio (Lot 1: Lot 2: Lot 3: placebo).

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. The vaccine is

provided as a sterile lyophilized powder in a dosage strength of 200 μg/dose (total for toxoids A and B) given at Month 0, Month 1, and Month 6. The vaccine will be reconstituted with AlOH diluent immediately before use as instructed in the investigational product (IP) manual. The AlOH diluent is supplied as a 1-mg aluminum/mL (as AlOH) liquid suspension.

Placebo

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

Statistical Methods

The study sample size estimate is based on the study primary immunogenicity objective to demonstrate lot-to-lot consistency, by evaluating the toxin A– and toxin B–specific neutralizing antibody in terms of GMCs, 1 month after the third vaccination (Month 7). A 2-fold equivalence margin is used as the criterion; 263 evaluable subjects per lot will provide an overall 90% power to declare equivalence between all 6 comparisons for both toxin A and toxin B.

Assuming a maximum study nonevaluable rate of 20%, a total of 1316 subjects need to be enrolled in the study to meet the primary objective, with a randomization ratio of 1:1:1:1 (Lot 1: Lot 2: Lot 3: placebo).

The primary immunogenicity objective of the lot-to-lot consistency will be achieved if the 2-sided 95% confidence intervals (CIs) on the GMC ratios for all 6 comparisons are within the interval (0.5, 2), for both toxin A and toxin B.

All safety and reactogenicity endpoints will be summarized as proportions of subjects with events by vaccine group. Additionally, exact 2-sided 95% CIs for proportions will be provided as applicable.

For immunogenicity endpoints, GMCs and geometric mean fold rises (GMFRs) from baseline will be calculated by vaccine group along with the 95% CIs for both toxin A and toxin B.

SCHEDULE OF ACTIVITIES

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

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

Visit ID	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Visit Description	**Month 0 (Vax 1)**	**Month 1 (Vax 2)**	**Month 2 (Phone Contact)**	**Month 6 (Vax 3)**	**Month 7**
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**
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	
Discuss contraceptive use[b]	X	X	X	X	
Confirm eligibility[b]	X	X	X	X	X
Review temporary delay criteria[a]	X	X		X	
Randomization[a]	X				
Blood draw for immunogenicity assessment[b]	X				X[c]
Vaccination	X	X		X	
Postvaccination observation (at least 30 minutes) and AE assessment	X	X		X	
Issue measuring device and thermometer, and provide instructions on their use, as required	X	X		X	
Assist the subject with downloading the app, or issue provisioned device	X				
Review e-diary completion requirements	X	X		X	
Record AEs/SAEs	X	X	X	X	X
Telephone contact			X		
Review e-diary data[d]	←	—	—	—	→
Collect e-diary					X

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

a. Prior to vaccination.
b. Prior to vaccination, if at a vaccination visit.
c. Any AEs occurring up to 48 hours after blood draw must be recorded on the case report form (CRF).
d. E-diary data review is ongoing during subject e-diary data-entry periods (7 days after each vaccination) via an internet-based portal.

1. INTRODUCTION

1.1. Mechanism of Action/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.

1.2. Background and Rationale

1.2.1. *Clostridium difficile* Disease Background

C difficile, a gram-positive anaerobic, spore-forming bacillus, is the main cause of nosocomial infectious diarrhea in industrialized countries.[1,2,3,4,5] 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.[6] *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.[7] As many as 50% or more of hospital patients colonized by *C difficile* are asymptomatic carriers.[6]

C difficile can produce 3 toxins, toxin A (TcdA), toxin B (TcdB), and binary toxin.[8] TcdA and TcdB are the principal virulence factors for CDI,[9] causing severe inflammation in the bowel.[10,11] 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.[2,12]

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.[13]

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.[11,14,15,16,17] 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.[11,18,19] Additional risk factors for recurrence include failure to mount an immune response to TcdA and/or TcdB and infection with a hypervirulent strain.[20,21]

Increased incidence and severity of the disease with associated complications, colectomy rates, and mortality have been observed over the last 10 to 20 years.[22,23,24] In Europe, increased mortality, prolonged length of hospital stay, and incremental cost of hospitalization in association with CDI have been reported.[25,26] A systematic review published in 2012 reported 30-day mortality estimates in Europe ranging from 6.8% to 42%.[26] In a surveillance study conducted in the United States, approximately 453,000 cases of CDI and approximately 29,000 deaths were reported in 2011.[27] 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.[28,29]

In the last decade, the numbers and severity of *C difficile* iatrogenic outbreaks in hospitals and nursing homes have increased.[27,28,30] Key factors in this escalation include emergence of hypervirulent pathogenic strains such as BI/NAP1/027,[31,32,33] increased use of antibiotics,[34] improved detection methods, and increased exposure to spores in healthcare facilities.[35]

Metronidazole has been recommended as initial therapy since the late 1990s, but recent guidance issued by the Infectious Diseases Society of America (IDSA) recommends either vancomycin or fidaxomicin as the first choice, and metronidazole should be used only if they are not available.[6,21,36,37] 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.[19] European guidelines for treatment of CDI include fidaxomicin as an option for treatment of recurrence.[21] Fecal transplantation has also been shown to be effective in some patients for the treatment of multiple recurrences of CDI.[38,39] However, regulatory oversight of this method remains in development,[40] 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.[41]

1.2.2. *Clostridium difficile* Vaccine Development Rationale

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.[20,42,43,44] Preclinical studies have shown that active immunization with inactivated toxins ("toxoids") and passive immunization with antitoxin antibodies protect animals from lethal challenge.[45,46,47] 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.[48] Results of human studies 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.[49]

To date, there is no approved vaccine to prevent primary or recurrent CDI. There are at least 2 other vaccines in development that target *C difficile* toxins. A toxoid-based vaccine adjuvanted with aluminum hydroxide (AlOH) has been evaluated in Phase 1 and 2 studies,[50,51,52,53] and efficacy is currently being evaluated in a Phase 3 study.[54] The other is a recombinant fusion protein comprising fragments of the receptor-binding domains of TcdA and TcdB separated by a 4–amino acid linker;[55] this vaccine has been evaluated in a completed Phase 2 study.[56]

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

1.2.3. *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.

1.2.3.1. Nonclinical Development

In nonclinical 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. In nonhuman primates, Pfizer's toxoid vaccine formulations with and without AlOH induced robust neutralizing antitoxin antibody responses to both TcdA and TcdB. The nonclinical data generated by Pfizer in rhesus macaques support the use of a 3-dose regimen of the *C difficile* vaccine, with or without AlOH.

1.2.3.2. 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.[57] 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. Adverse events (AEs) were reported in all vaccine groups, with little difference in the number of subjects between the dose groups and the placebo group or between vaccine formulations. In subjects who received the vaccine formulations, both the toxin A– and toxin B–specific neutralizing antibody geometric mean concentrations (GMCs) increased substantially at 1 month after Dose 2 and after Dose 3 compared to baseline. Potent antitoxin neutralizing responses were evident in immunized subjects 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.

Based on these data, a Phase 2 study (B5091003) was initiated using a 3-dose regimen (Days 1, 8, and 30) and 2 antigen dose levels (100 and 200 μg) of the toxoids alone

reconstituted with sodium chloride diluent. However, recruitment and vaccinations were halted because of the occurrence of 7 cases of Grade 3 injection site redness after Dose 2. In light of this observed tolerability profile, the decision was made to progress development of the AlOH-containing formulation into a second Phase 2 study. This Phase 2 study (B5091009) of the AlOH-containing formulation is ongoing to assess the safety, tolerability, and immunogenicity of 2 antigen dose levels (100 and 200 μg) and two 3-dose regimens (Days 1, 8, and 30 and Months 0, 1, and 6). A prespecified interim analysis of data up to Month 7 from this study demonstrated that the immunogenicity profile following 3 doses administered at Months 0, 1, and 6 was superior to that when the doses were administered at Days 1, 8, and 30. In addition, the 200-μg dose level was more immunogenic than the 100-μg dose level. On this basis, it was decided to progress into Phase 3 development with the 200-μg dose level administered at Months 0, 1, and 6.

The ongoing Phase 3 efficacy study (B5091007) is a placebo-controlled, randomized (1:1, vaccine:placebo), observer-blinded, parallel-group study in subjects 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 present study (B5091008) is a Phase 3, placebo-controlled, randomized, 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. The study seeks to recruit a relatively healthy population in an age category that is harmonized with the previous Phase 2 study (B5091009). The Phase 2 study provides significant information pertaining to immunological and safety responses, and immunological variability, particularly 1 month after Dose 3. 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.

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

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Immunogenicity Objective:	**Primary Immunogenicity Endpoint:**
• To demonstrate that the immune responses induced by 3 lots of *C difficile* vaccine are equivalent as measured by *C difficile* toxin A– and toxin B–specific neutralizing antibody levels 1 month after the third vaccination when administered in a 3-dose regimen to healthy adults 65 to 85 years of age.	• *C difficile* toxin A– and toxin B–specific neutralizing antibody levels for each lot, expressed as GMCs (neutralization units/mL) at Month 7.
Primary Safety Objective:	**Primary Safety Endpoints:**
• To evaluate the safety of *C difficile* vaccine when administered in a 3-dose regimen to healthy adults 65 to 85 years of age, as measured by the number and percentage of subjects reporting local reactions and systemic events, adverse events, and serious adverse events.	• Local reactions (pain, erythema, and induration), as self-reported in electronic diaries (e-diaries) for up to 7 days following each dose of investigational product. • Systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain), as self-reported in e-diaries for up to 7 days following each dose of investigational product. • Nonserious adverse events from signing of the informed consent document (ICD) to 1 month after receipt of the third dose of investigational product. • Serious adverse events from signing of the ICD to 1 month after receipt of the third dose of investigational product.
CCI [redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

This is a Phase 3, placebo-controlled, randomized, observer-blinded study to evaluate the lot consistency, safety, tolerability, and immunogenicity of an AlOH-containing *C difficile* vaccine (200 µg total toxoid) administered as a 3-dose regimen at Months 0, 1, and 6 in healthy adults 65 to 85 years of age.

Subjects will be randomized into 1 of 4 groups in a 1:1:1:1 ratio (Lot 1: Lot 2: Lot 3: placebo).

3.1. Approximate Number of Subjects

Approximately 1316 healthy adults, 65 to 85 years of age, will be enrolled.

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

3.2. Approximate Duration of Subject Participation

Subjects will be followed for 1 month after receipt of their third vaccination. Therefore, individual subjects will participate in the study for approximately 7 months.

3.3. Approximate Duration of the Study

This study will be completed in approximately 16 months.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

1. Evidence of a personally signed and dated ICD indicating that the subject has been informed of all pertinent aspects of the study.

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

3. Healthy adults 65 to 85 years of age at enrollment (signing of the ICD) as determined by medical assessment, and the clinical judgment of the investigator, to be eligible for the study. Subjects with preexisting chronic medical conditions determined to be stable may be included.

4. Male subjects or female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):

    a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a nonstudy serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Have medically confirmed ovarian failure.

All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

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

4.2. Exclusion Criteria

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

1. 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 subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

2. Participation in other studies involving investigational drug(s)/vaccine(s) within 28 days prior to study entry through conclusion of the study.

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

4. Proven or suspected prior episode of CDI.

5. Unstable chronic medical condition or disease requiring significant change in therapy or hospitalization for worsening disease within 8 weeks before receipt of investigational product.

6. Serious chronic medical disorders, including metastatic malignancy, severe chronic obstructive pulmonary disease (COPD) requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease, or any other disorder that in the investigator's opinion precludes the subject from participating in the study.

7. Any bleeding disorder or anticoagulant therapy that would contraindicate intramuscular injection.

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

9. Subjects who may be unable to respond to vaccination due to:

    - Congenital or acquired immunodeficiency.

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

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

- Underlying bone marrow disorder such as myelodysplasia, myeloma, or myeloproliferative disorder, treated within the past year, or any history of bone marrow transplant.

- Malignancy that required treatment with chemotherapy (including the use of adjunctive and hormonal therapy), immunotherapy, radiation therapy, or antineoplastic target therapies within the past 24 months.

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

11. Residence in a nursing home or other long-term care facility, or requirement for semiskilled nursing care or assisted living. An ambulatory subject who lives in an autonomous manner in a retirement home or village is eligible for the trial.

12. A known infection with human immunodeficiency virus (HIV).

13. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavioral or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

14. Female subjects of childbearing potential; pregnant female subjects; breastfeeding female subjects; fertile male subjects who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

4.3. Criteria for Temporarily Delaying Vaccine Administration

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

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

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

3. If systemic corticosteroids have been administered short term (≤7 days) for treatment of an acute illness, investigational product administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled, intra-articular/intrabursal, or topical corticosteroids are permitted.

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

4.4. Lifestyle Requirements

4.4.1. Contraception

All fertile male subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the vaccination period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the schedule of activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects 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 subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the partner.

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

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets the criteria for nonchildbearing potential, as described below:

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    - Have medically confirmed ovarian failure; or

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.5. 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 study reference manual (SRM).

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study 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 subject'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 subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. INVESTIGATIONAL PRODUCTS

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

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 3 lots of *C difficile* vaccine will appear identical and all site personnel will be blinded to lot allocation.

5.1. Allocation to Investigational Product

Allocation of subjects 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 1:1:1:1 to each of the lots and control group. 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 subject number. They will then be provided with a randomization number, vaccine assignment, and dispensable unit (DU) or container number. The IRT system will provide a confirmation report containing the subject 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.

5.2. Blinding of Site Personnel

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

The principal investigator will assign the responsibility of the unblinded dispensers/administrators to persons who will not participate in the evaluation of any study subject. To ensure adequate coverage, at least 2 unblinded dispensers/administrators will be assigned per site. Members of the study site staff or clinic pharmacy should fulfill these roles. Contact between the unblinded dispensers and study subjects should be kept to a minimum. The investigator, study coordinator, and any site staff other than the unblinded dispensers/administrators must not be allowed to know the investigational product assigned to any study subject and must not be allowed to see the investigational product container contents.

5.3. Blinding of the Sponsor

Those study team members who are involved in ensuring that protocol requirements for investigational product handling, allocation, and administration are fulfilled at the site (eg, the unblinded Pfizer clinician [separate from the study team], clinical research associates [CRAs]) will be unblinded for the duration of the study. All other study team members and all laboratory personnel performing the serology assays will remain blinded to vaccine assigned/received throughout the study.

5.4. Breaking the Blind

The study will be subject and investigator blinded.

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 subject. 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 case report form (CRF).

5.5. Subject Compliance

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

5.6. Vaccine Supplies

5.6.1. Formulation and Packaging

5.6.1.1. *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. The vaccine is provided as a sterile lyophilized powder in a dosage strength of 200 μg/dose (total for toxoids A and B). The vaccine will be reconstituted with AlOH diluent immediately before use as instructed in the investigational product (IP) manual. The AlOH diluent is supplied as a 1-mg aluminum/mL (as AlOH) liquid suspension.

Blinded, sealed cartons will contain 1 single-use vial of *C difficile* vaccine lyophilized powder for reconstitution and 1 single-dose syringe of AlOH diluent. The total volume of resuspended vaccine to be injected is 0.5 mL per dose.

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.

5.6.1.2. Placebo

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

5.6.2. Preparation and Dispensing

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

5.6.3. Administration

All injections will be administered in the upper deltoid muscle, preferably of the nondominant arm, by the **unblinded** administrator. The size of the needle used for administration will be based on the subject's weight at the time of enrollment. Refer to the IP manual for additional information.

Subjects will receive 1 dose of *C difficile* vaccine/placebo at Visits 1 (Month 0), 2 (Month 1), and 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 CRF.

5.7. Investigational Product Storage

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

Investigational products should be stored in their original containers and in accordance with the labels.

See the IP manual for storage conditions of the product once reconstituted.

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

The investigational vaccine, AlOH diluent, and placebo will be shipped at +2°C to +8°C to each study site after required regulatory and legal documents have been received by the sponsor. Upon receipt at the study site, the products should be immediately transferred to a +2°C to +8°C temperature-monitored refrigerator for storage.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all nonworking days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

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

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

5.8. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.8.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the 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.

5.9. Concomitant Medication(s)

5.9.1. Recording Concomitant Vaccinations and Medications

Subjects will be asked to provide a history with the name(s) and date(s) for all vaccinations received from 28 days prior to enrollment until completion of the study. No additional concomitant medications will be recorded.

5.9.2. Prohibited Concomitant Vaccinations and Medications

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 anticoagulant therapy that would contraindicate intramuscular injection from enrollment through the last dose of investigational product.

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

Receipt of systemic corticosteroids (≥20 mg/day of prednisone or equivalent) for ≥14 days is prohibited from 28 days prior to enrollment until completion of the study.

Receipt of chemotherapy for a malignancy (including the use of adjunctive and hormonal therapy), immunotherapy, radiation therapy, or antineoplastic target therapies within the past 24 months until completion of the study.

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

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

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.

5.9.3. Permitted Concomitant Medications

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

Medication, other than that described as prohibited in Section 5.9.2, required for treatment of preexisting stable conditions is permitted.

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

6. STUDY PROCEDURES

6.1. Study Period

6.1.1. Visit 1: Month 0 – Vaccination 1 (Day 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 subject's demography (including date of birth, sex, race, and ethnicity). The 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 are met (Section 4). 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 subject, perform a physical examination and record the findings.

- Record nonstudy vaccines as described in Section 5.9.1.
- Measure and record the subject's weight and height.
- Measure and record the subject's oral temperature.
- Discuss contraceptive use.
- Ensure that all inclusion criteria, none of the exclusion criteria, and none of the temporary delay criteria are met (Section 4).
- An appropriate site staff member (may be blinded or unblinded) will use the IRT system to obtain the subject's randomization number and investigational product blinded carton number.
- Collect a blood sample of approximately 20 mL for immunogenicity testing (Section 7.2).
- Unblinded site staff will prepare and administer investigational product. Investigational product will be administered by intramuscular 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 subject 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 serious adverse events (SAEs) (relative to the time of vaccination) as described in Section 8 and the schedule of activities.
- Issue a measuring device for measurement of local reactions, and a digital thermometer for recording daily temperatures. Provide instructions on their use and recording.
- Explain the requirements for the completion of the e-diary and assist the subject in downloading the study application (app) onto the subject's own device or issue a provisioned device (see Section 7.1). Provide instructions and ask the subject to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- Ask the subject to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Schedule an appointment for the subject to return for the next study visit.

- Complete the source documents.
- Complete the CRF.
- Review the e-diary data online following vaccination to evaluate subject compliance and as part of the ongoing safety review.

6.1.2. 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 subject's e-diary data and follow up on any ongoing local reactions or systemic events.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 6.2.
- 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 and the schedule of activities. Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines as described in Section 5.9.1.
- Measure and record the subject's oral temperature.
- Discuss contraceptive use.
- Ensure that none of the temporary delay criteria are met (Section 4.3).
- An appropriate site staff member (may be blinded or unblinded) will use the IRT system to obtain the subject's investigational product blinded carton number.
- Unblinded site staff will prepare and administer investigational product. Investigational product will be administered by intramuscular 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 subject 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.

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

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

- Schedule an appointment for the next study visit.

- Complete the source documents.

- Complete the CRF.

6.1.3. Visit 3: Month 2 (28 to 42 Days After Visit 2)

- Contact the subject 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 and the schedule of activities. Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.

- Follow up on any ongoing local reactions or systemic events.

- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 6.2.

- Record nonstudy vaccines as described in Section 5.9.1.

- Discuss contraceptive use.

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

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

- Complete the source documents.

- Complete the CRF.

6.1.4. Visit 4: Month 6 – Vaccination 3 (140 to 168 Days After Visit 2)

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

- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 6.2.

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

- Record nonstudy vaccines and as described in Section 5.9.1.

- Measure and record the subject's oral temperature.

- Discuss contraceptive use.

- Ensure that none of the temporary delay criteria are met (Section 4.3).

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

- Unblinded site staff will prepare and administer investigational product. Investigational product will be administered by intramuscular 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 subject 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.

- Ensure the subject 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.

- Remind the subject to complete the e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.

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

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

- Complete the source documents.

- Complete the CRF.

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

- Review the subject's e-diary data and follow up on any ongoing local reactions or systemic events.
- Collect the subject's e-diary device, if applicable.
- Ensure that the subject continues to be eligible for the study and does not meet any of the withdrawal criteria as described in Section 6.2.
- 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 and the schedule of activities. Review AEs that were ongoing from the previous visit and record their stop dates or confirm if they are still continuing.
- Record nonstudy vaccines as described in Section 5.9.1.
- Collect a blood sample of approximately 20 mL for immunogenicity testing (Section 7.2). Any AEs occurring up to 48 hours after blood draw must be recorded on the CRF.
- Complete the source documents.
- Complete the CRF.

6.1.6. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction (Section 7.1.1.2), systemic event (Section 7.1.1.3), or fever (Section 7.1.1.4) is reported in the e-diary data, 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 7.1.1.2), systemic event (Section 7.1.1.3), or fever (Section 7.1.1.4) 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 subject's local reaction as Grade 4.

6.2. Subject Withdrawal

Subject eligibility must be confirmed at each visit by an appropriate member of the investigator's study team as described in Sections 4 and 5.9.2. If a subject is discontinued from vaccination and the subject consents, safety follow-up will be conducted for 1 month after the last dose of vaccine.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the

inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

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

7. ASSESSMENTS

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

7.1. Safety Assessments

Safety parameters will be assessed as described in the schedule of activities, Section 6, Section 8, and below.

A clinical assessment, including medical history, will be performed on all subjects 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.

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 within 7 days after investigational product administration. These prospectively collected occurrences of local reactions and systemic events are graded as described in Section 7.1.1.

7.1.1. Electronic Diary

Subjects 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 from Day 1 to Day 7, with Day 1 being the day of vaccination, following each vaccination. The e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the subject's experience at that time. Data on local reactions 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 subject e-diary data-entry periods (from Day 1 to Day 7, with Day 1 being the day of vaccination) via an internet-based portal.

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

7.1.1.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.[58]

7.1.1.2. Local Reactions

During the e-diary reporting period, subjects will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the e-diary. If a local reaction persists beyond the end of the e-diary period following vaccination, the subject will be requested to report that information. 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 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the vaccine injection site will be assessed by the subject as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the e-diary, the site should contact the subject by telephone 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 subject's local reaction as Grade 4. If a subject 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 subject. The Grade 4 reaction must be recorded in the CRF and is not collected in the e-diary.

Table 1. 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

7.1.1.3. Systemic Events

During the e-diary reporting period, subjects 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 subject as absent, mild, moderate, or severe according to the grading scale in Table 2.

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 subject's systemic event as Grade 4. If a subject 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 subject. The Grade 4 reaction must be recorded in the CRF and is not collected in the e-diary.

Table 2. 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

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
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.

7.1.1.4. Fever

In order to record information on fever, a digital thermometer will be given to subjects 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 3.

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 subject's fever as Grade 4. If a subject 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 subject. The Grade 4 reaction must be recorded in the CRF.

Table 3. 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)

7.2. Immunogenicity Assessments

Serum samples will be obtained for immunogenicity testing at Visit 1 (Month 0, immediately before Dose 1) and Visit 5 (Month 7, 1 month after Dose 3).

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 to allow for adequate volume required for repeat testing or additional antigen-specific immunogenicity testing to be performed.

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

7.3. 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 subject'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 subject's genetic material will be performed.

The subject 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 subject's genetic material is performed.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety 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.

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	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a nonleading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject'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 subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject 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.

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.

8.1.4.2. Recording Nonserious AEs and SAEs on the CRF

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

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and nonserious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the

investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

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

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

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

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

8.2.3. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

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

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

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

8.3. Severity Assessment

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 subject's usual function.
2	MODERATE	Interferes to some extent with subject's usual function.
3	SEVERE	Interferes significantly with subject's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects 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 subject 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 subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 subject 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, 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, alkaline phosphatase, and acetaminophen drug and/or protein adduct levels. 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) 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.

8.4.3. Exposure to the Investigational Product 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.

8.4.3.1. Exposure During Pregnancy

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 subject or subject's partner becomes or is found to be pregnant during the subject'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 subject 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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. 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.

8.4.3.3. 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 subject 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.

8.4.4. Medication Errors

Other 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

8.4.4.1. Medication Errors

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

Medication errors include:

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

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.

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**.

8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be reported by a member of the unblinded site staff as described in the IP manual. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

9. DATA ANALYSIS/STATISTICAL METHODS

A detailed methodology for summary and statistical analysis of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be finalized before the start of any analyses and will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will be reflected both in the amended protocol and in the SAP. The SAP amendment will follow the protocol amendment.

9.1. Sample Size Determination

In order to meet the immunogenicity primary objective, the study sample size estimate is based upon the evaluation of lot-to-lot consistency on the toxin A– and toxin B–specific neutralizing antibody in terms of GMCs, 1 month after the third vaccination (Month 7). A 2-fold equivalence margin is used for the study. Assuming the inherent difference for toxin A– and toxin B–specific neutralizing antibody responses is no more than 0.2 (in logarithmic scale) between any 2 lots, and the common standard deviations for toxin A– and toxin B-specific neutralizing antibodies are 0.899 and 1.485 (natural log value), respectively (based on the standard deviations for toxin A and toxin B at Month 7 in Study B5091009), a sample size of 263 evaluable subjects per lot will provide an overall 90% power to declare equivalence between all 6 comparisons for both toxin A and toxin B (see Table 4).

Table 4. Power Analysis (Primary Immunogenicity Endpoint)

Criteria	Neutralizing Antibody	Standard Deviation (Log Value)	Assume Observed Log GMC Difference	Number of Evaluable Subjects per Lot	Power[a]	Overall Power (3 Comparisons for Each Toxin)
95% CI for GMC ratio (any 2 lots) is between 0.5 and 2.0	Toxin A	0.899	0.2	263	>99.99%	>99.99%
	Toxin B	1.485	0.2	263	96.72%	90.47%
	Overall power (to meet equivalence for both toxin A and toxin B)					90.47%

a. Using a 2-fold equivalence margin for GMC ratios at a 2-sided, 0.05 alpha level.

Assuming a maximum nonevaluable rate of approximately 20%, a total of 1316 subjects need to be enrolled to meet the primary objective, with a randomization ratio of 1:1:1:1 (Lot 1: Lot 2: Lot 3: placebo).

9.2. Immunogenicity Analysis

The immunogenicity data will be summarized according to the vaccine group (active vaccine and placebo) as received in the evaluable immunogenicity population, and according to the vaccine group as randomized in the modified intent-to-treat (mITT) population. Subjects receiving vaccine who did not follow their randomization assignment will be excluded from the evaluable immunogenicity population.

The *C difficile* toxin A– and toxin B–specific neutralizing antibody levels at each blood sampling time point will be summarized by GMCs (any *C difficile* toxin A– or toxin B-specific neutralizing antibody level that is below the lower limit of quantitation [LLOQ] will be assigned as 0.5 × LLOQ) and the associated 95% confidence intervals (CIs). The GMC will be calculated as the mean of the assay results after making the logarithm transformation and then back transformation to its original scale. Two (2)-sided 95% CIs will be constructed by back transformation of the CI for the mean of the logarithmically transformed assay results computed based on the Student's t distribution.

Exact 2-sided 95% CIs will be compiled using the Clopper-Pearson method for any proportions of subjects with *C difficile* toxin A– or toxin B–specific neutralizing antibody level ≥ cutoff (LLOQ).

9.2.1. Immunogenicity Analysis Population

An evaluable immunogenicity population and a mITT population will be defined for the immunogenicity analyses separately. The evaluable immunogenicity population will be the primary population for the immunogenicity analyses.

In general, the evaluable immunogenicity population will include all subjects who are eligible, receive the investigational product to which they are randomized, have blood drawn for assay testing within the specified time frame, have valid and determinate assay results for either toxin A or toxin B for the proposed analysis, and have no major protocol deviations.

The mITT population will include all randomized subjects who have received at least 1 vaccination and have at least 1 valid and determinate assay result for the proposed analysis.

9.2.2. Analysis of the Primary Immunogenicity Endpoint

The primary objective of lot consistency will be tested at 1 month after Dose 3 for each *C difficile* toxin A– or toxin B–specific neutralizing antibody. The evaluable immunogenicity population will be used for lot-consistency hypothesis testing.

The null hypothesis (H_0) for the lot consistency is:

$$H_0 : \left| \ln(\mu_1)–\ln(\mu_2) \right| \geq \ln(2) \text{ OR } \left| \ln(\mu_1)–\ln(\mu_3) \right| \geq \ln(2) \text{ OR } \left| \ln(\mu_2)–\ln(\mu_3) \right| \geq \ln(2)$$

where $1n(\mu_1)$, $1n(\mu_2)$, and $1n(\mu_3)$ are the means of the natural logarithm-transformed data of the *C difficile* toxin A– or toxin B–specific neutralizing antibody concentration from subjects receiving *C difficile* vaccine from Lots 1, 2, and 3, respectively, measured 1 month after the third vaccination (Month 7) with *C difficile* vaccine. The neutralizing antibody concentration data will be logarithmically transformed for analysis. GMC ratios, along with 95% CIs, will be computed for each toxin A– or toxin B–specific neutralizing antibody concentration for any 2 of the 3 lots (a total of 6 comparisons).

The primary immunogenicity objective of the lot-to-lot consistency will be achieved if the 2-sided 95% CIs on the GMC ratios for all 6 comparisons are within the interval (0.5, 2), for both toxin A and toxin B.

CCI [redacted]

CCI [redacted]

[redacted]

9.3. Safety Analysis

The safety population will include all subjects who receive at least 1 dose of an investigational product. For the safety analysis, subjects will be analyzed according to the investigational product received. A descriptive summary will be presented for each vaccine lot, the combined vaccine lots, and the control group. For Tier 1 and Tier 2 events, the comparison between the pooled lots and control group will be performed.

Point estimates and the exact 2-sided 95% CIs will be compiled using the Clopper-Pearson method for proportions of subjects reporting each event.

The proportions of subjects 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 signing of the ICD to 1 month after receipt of the third dose of investigational product. SAEs will be summarized by vaccine group from signing of the ICD to 1 month 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 subjects experiencing at least 1 event and the number of events for each vaccine group, and the exact 2-sided 95% CIs.

The 3-tier approach will be used for the AE summary. Detailed analysis of each tier will be described in the SAP.

9.4. Analysis Timing

No interim analysis is planned for this study.

The final analysis will be performed after all the safety and serology data are available.

9.5. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter. The E-DMC may review unblinded data during closed meeting sessions; however, the sponsor will remain blinded (with the exception of the unblinded

clinician who is independent of the study team) and will not be permitted access to the randomization assignments until the database is locked and unblinded.

The E-DMC will review safety data at defined intervals as specified in the charter. The E-DMC may conduct additional meetings to review safety data at other time points during the study, at its discretion, or at the request of the sponsor. In addition, as determined by the sponsor clinician, the E-DMC may meet on an ad hoc basis to evaluate any SAEs related to vaccination, or related AEs that may jeopardize further subject participation, in order to determine that the study may be continued safely.

After each meeting, the E-DMC will make recommendations that may include the following: continue the study with or without modification; or pause or stop vaccination for safety or other reasons.

The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed ICDs, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

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

The ICDs used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

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

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

12.4. 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as database lock.

14. SPONSOR DISCONTINUATION CRITERIA

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

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 28 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (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 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

Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (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 subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

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 synopses in which any data that could be used to identify individual patients has 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.

15.2. Publications by Investigators

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

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

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

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

all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

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

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

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

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Appendix 1. Abbreviations

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

Abbreviation	Term
AE	adverse event
AlOH	aluminum hydroxide
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CBER	Center for Biologics Evaluation and Research
CDI	*Clostridium difficile* infection
CI	confidence interval
CK	creatine kinase
COPD	chronic obstructive pulmonary disease
CRA	clinical research associate
CRF	case report form
CSA	clinical study agreement
CT	clinical trial
DILI	drug-induced liver injury
DU	dispensable unit
EC	ethics committee
e-diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	enzyme-linked immunosorbent assay
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
HIV	human immunodeficiency virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IDSA	Infectious Diseases Society of America
IgG	immunoglobulin G
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product

Abbreviation	Term
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N/A	not applicable
PCD	primary completion date
PFGE	pulsed-field gel electrophoresis
PI	principal investigator
PT	prothrombin time
RCDC	reverse cumulative distribution curves
SAE	serious adverse event
SAP	statistical analysis plan
SRM	study reference manual
SRSD	single reference safety document
TBili	total bilirubin
TcdA	*Clostridium difficile* toxin A
TcdB	*Clostridium difficile* toxin B
ULN	upper limit of normal
US	United States
VE	vaccine efficacy

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