CLINICAL STUDY REPORT SYNOPSIS

Vaccine Name and Compound Number: *Clostridioides difficile* Vaccine, Compound Number: PF 06425090

Report Title: Final Report: A Phase 3, Placebo-Controlled, Randomized, Observer-Blinded Study to Evaluate the Efficacy, Safety, and Tolerability of a *Clostridium Difficile* Vaccine in Adults 50 Years of Age and Older

Protocol Number: B5091007

Sponsor: Pfizer Inc.

Phase of Development: Phase 3

First Subject First Visit: 29 March 2017

Last Subject Last Visit: 21 December 2021

Coordinating Investigator(s): [redacted], MD

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Study Center(s): This study was conducted at 410 sites in multiple countries. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Date of Current Version: 16 August 2022

Date(s) of Previous Report(s): 27 July 2022

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OBJECTIVES

Study Objectives and Endpoints:

Clostridioides difficile infection (CDI) case definitions referred to in Table S1 are described in Appendix 1.

Table S1. Study Objectives and Endpoints

Primary Efficacy Objective(s):		**Primary Efficacy Endpoint(s):**

• To demonstrate that Pfizer's *Clostridium difficile* (*C difficile*) vaccine is effective in reducing the incidence of a first primary episode of CDI (case definition 1).[a]		• CDI incidence per 1000 person-years of follow-up, assessed during up to 2 time periods (each analysis was performed only if the preceding one was successful):
		  • After receipt of the third dose of investigational product onwards.
		  • After receipt of the second dose of investigational product onwards.

Primary Safety Objective(s):		**Primary Safety Endpoint(s):**
• To evaluate the safety profile of Pfizer's *C difficile* vaccine as measured by the percentage of participants reporting local reactions and systemic events, adverse events (AEs), and serious adverse events (SAEs).		• Local reactions (pain, erythema, and induration), as self-reported on electronic diaries (e-diaries) for up to 7 days following each dose of investigational product. • Systemic events (fever, vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain), as self-reported on e-diaries for up to 7 days following each dose of investigational product. • Nonserious AEs from the signing of informed consent document (ICD) to 1 month after receipt of the third dose of investigational product. • SAEs from the signing of the ICD to 6 months after receipt of third dose of investigational product.
Evaluation Order	**Secondary Objective(s):**	**Secondary Endpoint(s):**
	3-Dose Family	
1.	• To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing: • The incidence of all CDI cases (case definition 1 and case definition 2).	• CDI incidence per 1000 person-years of follow-up, assessed after receipt of the third dose of investigational product onwards.

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Table S1. Study Objectives and Endpoints

2.	• To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing the severity of CDI, defined by:
	  • The duration of CDI episodes.
	  • The requirement to seek medical attention.
		• Mean time to resolution of diarrhea in first primary episodes of CDI (case definition 1).
		• Proportion of participants experiencing a first primary episode of CDI (case definition 1) who had a non–protocol-related medically attended visit during the CDI episode.
		(Each analysis was performed only if the preceding one was successful).

3.	• To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing the incidence of recurrent CDI (case definition 2).	• CDI incidence per 1000 person-years of follow-up, assessed after receipt of the third dose of investigational product onwards.
	At-Least-2-Dose/Only-2-Dose Family	
1[b]	• To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing: • The incidence of all CDI cases (case definition 1 and case definition 2).	• CDI incidence per 1000 person-years of follow-up, assessed after receipt of the second dose of investigational product onwards.
2[b]	• To evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing the incidence of recurrent CDI (case definition 2).	• CDI incidence per 1000 person-years of follow-up, assessed after receipt of the second dose of investigational product onwards.

3[c]	• In participants who receive only 2 doses of vaccine, to evaluate the efficacy of Pfizer's *C difficile* vaccine in reducing:
	  • The incidence of a first primary episode of CDI (case definition 1).
	  • The incidence of recurrent CDI (case definition 2).
		• CDI incidence per 1000 person-years of follow-up.
		  • (Each objective was formally evaluated only if the preceding one was successful).

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[redacted]		
[redacted]		[redacted]

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Table S1. Study Objectives and Endpoints

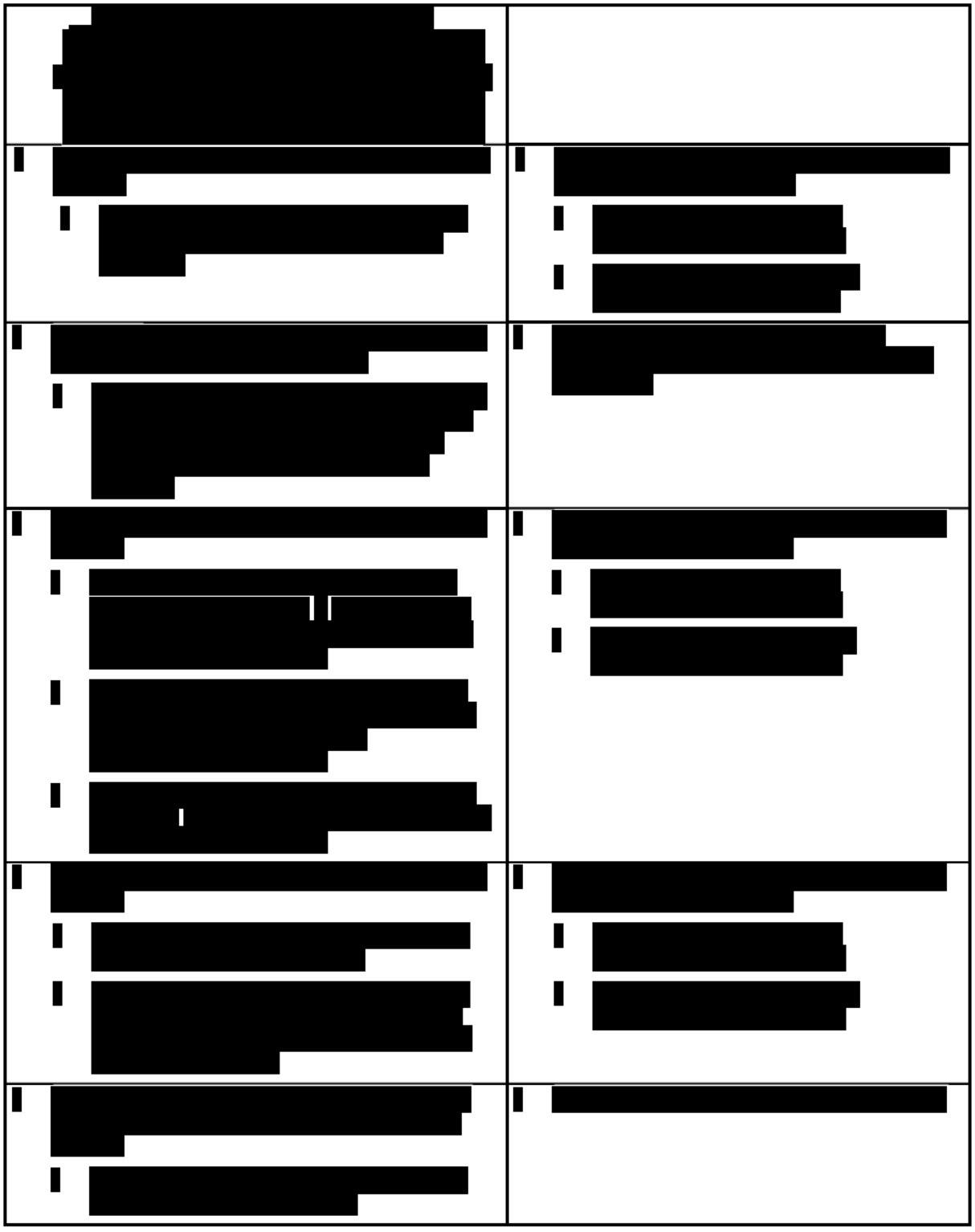

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Table S1. Study Objectives and Endpoints

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

a. Each participant may have contributed only once to the primary endpoint.
b. At-least-2-dose family.
c. Only-2-dose family.

METHODS

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

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

Participants were followed from the time they signed the ICD until sufficient cases had been accrued to declare efficacy or futility.

Inclusion/Exclusion Criteria:

Inclusion Criteria

Inclusion criteria were as follows:

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1. Evidence of a personally signed and dated ICD indicating that the participant was informed of all pertinent aspects of the study.

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

3. 50 Years or older at enrollment.

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

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

   or

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

   - At least 10 outpatient visits (primary and/or secondary care visits; defined as an in person visit to the office/clinic of a prescribing healthcare provider for the purposes of the diagnosis, treatment, or ongoing management of a medical condition, excluding pharmacy and mental health visits) in the previous 12 months; or

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

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

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

   - Or participants who received systemic (ie, oral or injected) antibiotics for a minimum of 48 hours at any time in the previous 12 weeks.

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

6. Negative urine pregnancy test for female participants of childbearing potential.

   Female participants of nonchildbearing potential must had met 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 serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state

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b. Had undergone a documented hysterectomy and/or bilateral oophorectomy

c. Had medically confirmed ovarian failure

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

Exclusion Criteria

Exclusion criteria were as follows:

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 participants who were 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 until Visit 5 (1 month after the third vaccination).

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

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

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

6. Participants who were unable to respond to vaccination because of:

Metastatic malignancy; or

End-stage renal disease (glomerular filtration rate <15 mL/min/1.73 m^2 or on dialysis); or

Any serious medical disorder that in the investigator's opinion was likely to be fatal within the next 12 months; or

Congenital or acquired immunodeficiency; or

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

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

7. Known infection with human immunodeficiency virus.

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

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

10. Prior small- or large-bowel resection (did not include appendectomy).

11. Any condition or treatment resulting in frequent diarrhea (≥3 loose stools per day more than once per month), as reported by the participant.

12. 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 have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

13. Pregnant female participants; breastfeeding female participants; fertile male participants and female participants of childbearing potential who were, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) and were unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol from the signing of the informed consent until at least 28 days after the last dose of investigational product.

Vaccines Administered: All injections were administered in the upper deltoid muscle, preferably of the nondominant arm, by the unblinded administrator. Participants received 1 dose of *C difficile* vaccine/placebo at Visits 1 (Month 0), 2 (Month 1), and 4 (Month 6).

A list of the investigational products administered in this study and their respective lot numbers is provided in Table S2.

Table S2. Investigational Product Lot Numbers

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number[a] (Pfizer)
Clostridium difficile vaccine	Pfizer	R56000	16-005448
Aluminum hydroxide diluent (1 mg/mL)	Pfizer	R52564	16-005447
Placebo (0.9% sodium chloride)	Pfizer	R30159	16-005048

a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.
Protocol B5091007 Investigational Product Lot Numbers Table – Final, Version 1.0, 13Oct2021.

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Efficacy Evaluations: Any time during the study period that a subject experienced passage of 3 or more unformed stools (Bristol stool chart types 5-7) within 24 hours, the subject was asked to collect the third or subsequent stool for provision to the central laboratory. The subject was provided with a sample collection kit and instructed on how to package the sample. The sample was shipped to a processing laboratory. The processing laboratory prepared aliquots of the stool for later analysis at the central laboratory.

Safety Evaluations: Participants recorded local reactions (redness, swelling, and pain at the injection site) and systemic events (vomiting, headache, fatigue, new or worsening muscle pain, and new or worsening joint pain) using an e-diary for 7 days following vaccination, which allowed recording of these assessments only within a fixed time window and provided an accurate representation of the participant's experience at that time.

AEs and SAEs were collected from the signing of the ICD through and including Visit 5 (Month 7) for AEs and through Visit 6 (Month 12) for SAEs.

Statistical Methods: The primary efficacy hypotheses were tested for null hypothesis vaccine efficacy (VE) ≤20% by a fixed sequence testing procedure, with a testing order of the first primary CDI cases (Case Definition 1) occurring from 14 days after receipt of the third dose, followed by those occurring from 14 days after receipt of the second dose. Secondary objectives for vaccine efficacy were evaluated with hypothesis tests sequentially with the order specified in Table S1. After accounting for multiplicity due to the interim and final analyses, as well as multiple endpoints, the type I error for the final analyses was adjusted to α of 0.018 (1-sided) for the primary efficacy endpoints and α of 0.009 (1-sided) for the secondary endpoints. Unadjusted α of 0.025 (1-sided) was used for exploratory endpoints. The corresponding 2-sided 96.4% confidence intervals (CIs), 98.2% CIs, and 95% CIs were presented for primary, secondary, and exploratory endpoints respectively. A null hypothesis would be rejected and the VE for the corresponding efficacy endpoint would be demonstrated if the lower bound of the 2-sided confidence interval for the VE >20%.

For endpoints involving the identification of 1 case per participant, the VE was defined as a percentage of VE = 100 × (1 – infection rate ratio [IRR]), where IRR was the infection rate ratio adjusted for surveillance time between the *C difficile* vaccine group and the placebo group. The corresponding VE confidence intervals were derived using the Clopper-Pearson method adjusted for surveillance time.

For endpoints involving the identification of 1 or more cases per participant, such as all episodes of CDI as defined by case definitions 1 and 2, VE and the corresponding confidence intervals were computed using a proportional means model.

The proportion of participants reporting local reactions at the injection site and systemic events on any day within the 7-day period after vaccination were descriptively summarized by vaccine group. Severities of local reactions and systemic events reported after each vaccination were also descriptively summarized by vaccine group. Two-sided 95% CIs based on the Clopper Pearson method were presented with the proportions.

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AEs were categorized according to Medical Dictionary for Regulatory Activities and summarized by vaccine group. All summaries of AEs showed the number and percentage of participants experiencing at least 1 event and the number of events for each vaccine group. Two-sided 95% CIs based on the Clopper-Pearson method were presented for (S)AE percentages. AEs were summarized using 3-tier methodology.

RESULTS

Subject Disposition and Demography:

A total of 17,535 participants were randomized to the study (8766 to the *C difficile* group and 8769 to the placebo group). Withdrawal by subject (~24% for each group) was the most frequent reason for withdrawal. Overall, 7894 (90.1%) participants in the *C difficile* group and 7967 (90.9%) participants in the placebo group completed the vaccination schedule (all 3 doses), and a total of 5533 (63.1%) participants in the *C difficile* group and 5574 (63.6%) in the placebo group completed the study.

The 2 vaccine groups in the safety population were generally similar with respect to demographic characteristics. Overall, 51.5% participants were female and 48.5% were male. The majority were White (79.2%) and from North America (65.1%); the mean age at randomization was 68 years. The 2 vaccine groups were also similar with regards to Charlson Comorbidity Index scores at baseline, with most participants scoring 0 (59.9% in the *C difficile* group and 59.7% in the placebo group) or 1 (25.9% in the *C difficile* group and 26.9% in the placebo group).

Efficacy Results:

Primary Endpoints

The vaccine efficacy of *C difficile* vaccine did not meet the primary objective for the reduction in the incidence of first episodes of primary CDI 14 days after receipt of the third dose of investigational product onwards: estimated VE of 31.0% with the lower bound of the 2-sided 96.4% CI being -38.7%, ≤ 20% (success criterion). Since the study failed to demonstrate vaccine efficacy for the first primary endpoint, hypothesis tests for all the subsequent vaccine efficacy endpoints were not performed per the pre-specified statistical analysis procedure. Estimates and associated 2-sided CIs for all the other efficacy endpoints were described.

The estimated vaccine efficacy for the second primary endpoint of reduction of primary CDI after receipt of the second dose of investigational product was 28.6% with the lower bound of the 2-sided 96.4% CI being -28.4%.

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Secondary Endpoints

In the 3-dose family, the first objective of reduction of the incidence of all CDI (Case Definitions 1 and 2) and the third objective of reduction of the incidence of recurrent CDI (Case Definition 2) were not met.

Although the primary endpoints did not meet success criteria, positive results were observed in the reduction of severity of CDI, as measured by reduction in duration of CDI episodes as well as the requirement to seek medical attention. Due to an outlier CDI episode with an extremely long duration in the placebo group, the median and the non-parametric Wilcoxon rank sum test were more appropriate statistics to compare the distributions of durations between the two groups. The median time to resolution of diarrhea in participants with a first primary episode of CDI ≥14 days after receipt of the third dose was 1 day in the *C difficile* group and 4 days in the placebo group, with a nominal Wilcoxon rank sum 2-sided p-value of 0.0172. This translates to a 75% reduction in median duration of disease episode. Duration of CDI episodes is a predictor of medically attended CDI. In a post hoc analysis of first primary episodes of CDI occurring at least 14 days after Dose 3 in the placebo group, the median duration of CDI episodes that were medically attended was 19 days compared with 2.5 days for CDI episodes for which medical attention was not sought, with a 2-sided p-value of 0.0024 based on Wilcoxon rank sum test.

For those participants with primary episodes of CDI, all participants that sought medical attention for their episodes were in the placebo group (11 cases in placebo), with an observed 100% VE (lower bound of the 2-sided 95% CI 59.6%) in a post hoc analysis. This indicates that the need for medical attention was completely reduced after *C difficile* vaccination, with protection extended from ≥14 days after Dose 3 for approximately 4 years.

In an additional post-hoc analysis, all participants that required antibiotics to treat their CDI episodes were all in the placebo group (10 cases in placebo), with an estimated VE of 100% (lower bound of the 2-sided 95% CI 54.8%), indicating that the *C difficile* vaccine significantly reduced antibiotic use in the treatment of first primary episodes of CDI.

Safety Results:

The proportions of participants who reported local reactions within 7 days after each dose and after any dose by maximum severity were similar.

The proportions of participants who reported any related AE from Dose 1 to 1 month after Dose 3 were 3.4% in the *C difficile* group compared to 1.7% in the placebo group. The difference relates to reactogenicity events that were also reported as adverse events seen mostly as nausea, injection site pain, redness and swelling, arthralgia, myalgia, and headache. The most commonly reported related system organ class (SOC) was general disorders and administration site conditions. Related AEs reported in ≥1% of participants within 1 month after vaccination were generally similar in both vaccine groups for each of the subgroup analyses by age group, race, ethnicity, gender, and region

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Tier 2 AEs with incidence rate of at least 1% in any vaccine group from Dose 1 to 1 month after Dose 3 were most commonly reported in the SOCs of gastrointestinal disorders, infections and infestations, injury, poisoning and procedural complications, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory, thoracic, and mediastinal disorders, and vascular disorders in the *C difficile* group. Falls were the most frequently reported AE in both groups. Nine hundred and eighteen AEs (10.5%) in the *C difficile* group were assessed as severe and potentially life threatening from the day of Dose 1 to 6 months after Dose 3.

The proportions of participants reporting any SAEs were low and similar (≤12.8%) in the *C difficile* and placebo groups from Dose 1 to 6 months after Dose 3, and <0.1% in both the *C difficile* and placebo groups for related SAEs.

The proportion of participants who experienced death from all causes was similar in both vaccine groups.

The proportion of participants who experienced diarrhea from all causes was similar in both vaccine groups.

Conclusions: Overall, Study B5091007 enrolled approximately 17,500 adults, 50 years of age and older. The study was expected to accrue 66 cases of CDI within 2 years of the primary vaccination series. Due to significant operational challenges created in part by the COVID-19 pandemic, the final analysis was performed at 42 cases within 4 years after agreement from the Food and Drug Administration (United States) to amend the protocol.

Although the vaccine did not have the expected impact on all primary CDI cases detected in this study, it was highly effective at preventing cases severe enough to require medical intervention. Importantly, outside the clinical trial setting, testing for *C difficile* must be requested by a healthcare professional, and CDI cases that are too mild to require medical attention are therefore never diagnosed or reported. Thus, the cases reported in surveillance and epidemiological studies are all, by definition, medically attended. Despite the study missing its primary endpoints, based on relevant secondary and post-hoc endpoints, the *C difficile* vaccine has the potential to provide major public health benefit by reducing the burden of CDI severe enough to require medical attention and associated antibiotic use.

The safety profile in over 8,700 participants who received a least one dose of Pfizer's *C difficile* vaccine was very well tolerated and showed a favorable safety profile.

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Appendix 1. CDI Case Definitions

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

Definition 1 – Primary Episode

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

Presence of diarrhea, defined as passage of 3 or more unformed stools (Bristol stool chart types 5-7) in 24 or fewer consecutive hours; and

Stool sample that is positive for the toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in the central laboratory.

or:

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

Definition 2 – Recurrent Episode

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

Presence of diarrhea, defined as passage of 3 or more unformed stools (Bristol stool chart types 5-7) in 24 or fewer consecutive hours; and

Stool sample that is positive for the toxin B gene (by PCR) and positive for toxin A and/or toxin B, as measured in the central laboratory.

or:

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

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