# Randomized Studies of Two *Clostridioides (Clostridium) Difficile* Vaccine Formulations


**Jody Lawrence,[1] Nicholas Kitchin,[2] Annaliesa S. Anderson,[3] Michael W. Pride,[3] Kathrin U. Jansen,[3] William C. Gruber,[3] Yahong Peng,[1] Kevin Yi,[1] Charles Knirsch,[3] Chris Webber[2]**

*[1]Pfizer Vaccine Clinical Research & Development, 500 Arcola Road, Collegeville, PA, USA; [2]Pfizer Vaccine Research & Development, Horizon Building, Honey Lane, Hurley, Berkshire SL6 6RJ, UK; [3]Pfizer Vaccine Research & Development, 401 N. Middletown Road, Pearl River, NY, USA*

For more information please contact:
Jody Lawrence, MD
Vaccine Clinical Research & Development
Pfizer Inc
Email: Jody.Lawrence@pfizer.com


## BACKGROUND

- *Clostridioides (Clostridium) difficile* is a gram-positive bacterium that has emerged as a major cause of diarrhea due to healthcare-associated and community-acquired infections.
- No licensed vaccine is currently available. Two formulations of investigational bivalent *C difficile* vaccine (QS-21 adjuvanted toxoid and toxoid-alone) were assessed for safety and immunogenicity in randomized, placebo-controlled, observer-blinded studies in healthy adults 50–85 years of age.

## METHODS

### QS-21 Study

- Phase 1 study, vaccine formulation consisting of 100-µg *C difficile* toxoids A and B (total toxoid content) adjuvanted with 50 µg of QS-21.
- Dosing schedules: administered on either Days 1, 8, and 30 (ie, day regimen) or Months 0, 1, and 3 (ie, shortened-month regimen).
- Subjects were enrolled in a 3:1 ratio to receive *C difficile* vaccine or placebo. Initially a small sentinel group of subjects 50–64 years of age were enrolled in the shortened-month regimen. Safety data were reviewed before enrolling a larger group of subjects 65–85 years of age in the shortened-month regimen simultaneously with enrollment of a smaller group of 50- to 64-year-old subjects in the day regimen.

### Toxoid-alone Study

- Phase 2 study, vaccine formulation consisting of 100- and 200-µg dose levels of a toxoid-alone formulation.
- Dosing schedule: administered on Days 1, 8, and 30 (ie, day regimen).
- Stage 1 included a sentinel cohort of 50- to 64-year-old subjects. Safety data from stage 1 were reviewed before the start of stage 2, which enrolled a 65- to 85-year-old cohort of subjects. In stages 1 and 2, randomization was performed in a 3:3:1 ratio of 100 µg *C difficile* vaccine, 200 µg *C difficile* vaccine, or placebo. Stage 3 was planned to occur after dose selection but was not initiated.

### Subjects

- In both studies, participants were healthy individuals 50–85 years of age; subjects with preexisting chronic conditions determined to be stable were eligible.

### Assessments

- Safety assessments constituted the primary outcomes for both studies and included numbers and percentages of subjects reporting local reactions (eg, redness, swelling, pain at the injection site) or systemic events (eg, fever, vomiting, diarrhea, headache, fatigue, new or worsening muscle pain, new or worsening joint pain) after each dose as reported via electronic diary. Safety assessments also included numbers and percentages of subjects reporting adverse events (AEs) and serious AEs (SAEs).
- Immunogenicity was assessed as a secondary endpoint for both studies using neutralization assays for toxins A and B.

## RESULTS

### Subjects

- Overall, 184 subjects were randomized in the QS-21 study, including 31 subjects in the 50- to 64-year age cohort shortened-month regimen who received 2 doses, 31 subjects in the 50- to 64-year age cohort day regimen who received 2 doses, and 120 subjects in the 65- to 85-year age cohort shortened-month regimen who received 1 dose.
- In the toxoid-alone study, 184 subjects were randomized, including 41 and 28 subjects in the 50- to 64-year and 65- to 85-year age cohorts, respectively, who received all 3 doses.
- Demographics are shown in **Table 1**.

**Table 1: Demographics**

| QS-21 Study | 50–64-Year Age Cohort: Shortened-Month Regimen Vaccine Group: Placebo (n=8) | 50–64-Year Age Cohort: Shortened-Month Regimen Vaccine Group: 100 µg *C diff* + QS-21 (n=24) | 50–64-Year Age Cohort: Day Regimen Vaccine Group: Placebo (n=8) | 50–64-Year Age Cohort: Day Regimen Vaccine Group: 100 µg *C diff* + QS-21 (n=24) | 50–64-Year Age Cohort: Total (N=64) | 65–85-Year Age Cohort: Day Regimen Vaccine Group: Placebo (n=30) | 65–85-Year Age Cohort: Day Regimen Vaccine Group: 100 µg *C diff* + QS-21 (n=90) | 65–85-Year Age Cohort: Total (N=120) |
|---|---|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | | | |
| Female | 1 (12.5) | 10 (41.7) | 6 (75.0) | 11 (45.8) | 28 (43.8) | 18 (60.0) | 53 (58.9) | 71 (59.2) |
| Male | 7 (87.5) | 14 (58.3) | 2 (25.0) | 13 (54.2) | 36 (56.3) | 12 (40.0) | 37 (41.1) | 49 (40.8) |
| Race, n (%) | | | | | | | | |
| White | 8 (100.0) | 24 (100.0) | 8 (100.0) | 24 (100.0) | 64 (100.0) | 26 (86.7) | 82 (91.1) | 108 (90.0) |
| Black | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (10.0) | 7 (7.8) | 10 (8.3) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (3.3) | 1 (1.1) | 2 (1.7) |
| Other | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ethnicity, n (%) | | | | | | | | |
| Non-Hispanic/non-Latino | 8 (100.0) | 24 (100.0) | 8 (100.0) | 24 (100.0) | 64 (100.0) | 30 (100.0) | 89 (98.9) | 119 (99.2) |
| Hispanic/Latino | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.1) | 1 (0.8) |
| Age at randomization, y | | | | | | | | |
| Mean (SD) | 55.5 (4.78) | 57.3 (4.31) | 55.3 (3.28) | 56.4 (3.87) | 56.5 (4.06) | 70.3 (4.05) | 71.1 (5.04) | 70.9 (4.81) |
| Median | 53.5 | 57.5 | 56.0 | 56.5 | 56.0 | 69.5 | 70.0 | 70.0 |
| Min, max | 50, 62 | 50, 63 | 51, 60 | 50, 63 | 50, 63 | 65, 81 | 65, 83 | 65, 83 |

| Toxoid-Alone Study | 50–64-Year Age Cohort (Day Regimen): Placebo (n=6) | 50–64-Year Age Cohort (Day Regimen): 100 µg *C diff* (n=18) | 50–64-Year Age Cohort (Day Regimen): 200 µg *C diff* (n=18) | 50–64-Year Age Cohort (Day Regimen): Total (N=42) | 65–85-Year Age Cohort (Day Regimen): Placebo (n=21) | 65–85-Year Age Cohort (Day Regimen): 100 µg *C diff* (n=61) | 65–85-Year Age Cohort (Day Regimen): 200 µg *C diff* (n=60) | 65–85-Year Age Cohort (Day Regimen): Total (N=142) |
|---|---|---|---|---|---|---|---|---|
| Sex, n (%) | | | | | | | | |
| Female | 1 (16.7) | 5 (27.8) | 9 (50.0) | 15 (35.7) | 13 (61.9) | 37 (60.7) | 36 (60.0) | 86 (60.6) |
| Male | 5 (83.3) | 13 (72.2) | 9 (50.0) | 27 (64.3) | 8 (38.1) | 24 (39.3) | 24 (40.0) | 56 (39.4) |
| Race, n (%) | | | | | | | | |
| White | 4 (66.7) | 12 (66.7) | 13 (72.2) | 29 (69.0) | 19 (90.5) | 57 (93.4) | 52 (86.7) | 128 (90.1) |
| Black | 2 (33.3) | 5 (27.8) | 5 (27.8) | 12 (28.6) | 2 (9.5) | 4 (6.6) | 5 (8.3) | 11 (7.7) |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.7) | 1 (0.7) |
| Other | 0 (0.0) | 1 (5.6) | 0 (0.0) | 1 (2.4) | 0 (0.0) | 0 (0.0) | 2 (3.3) | 2 (1.4) |
| Ethnicity, n (%) | | | | | | | | |
| Non-Hispanic/non-Latino | 6 (100.0) | 17 (94.4) | 17 (94.4) | 40 (95.2) | 20 (95.2) | 59 (96.7) | 57 (95.0) | 136 (95.8) |
| Hispanic/Latino | 0 (0.0) | 1 (5.6) | 1 (5.6) | 2 (4.8) | 1 (4.8) | 2 (3.3) | 3 (5.0) | 6 (4.2) |
| Age at randomization, y | | | | | | | | |
| Mean (SD) | 55.0 (4.34) | 56.3 (4.39) | 54.8 (4.03) | 55.5 (4.19) | 71.4 (4.99) | 71.5 (4.63) | 71.0 (5.25) | 71.3 (4.93) |
| Median | 53.0 | 56.5 | 54.5 | 55.0 | 71.0 | 70.0 | 70.5 | 71.0 |
| Min, max | 52, 63 | 50, 63 | 50, 61 | 50, 63 | 65, 82 | 65, 85 | 65, 85 | 65, 85 |

## RESULTS (continued)

### Local Reactions and Systemic Events

- In the day regimen, 10 reports across both studies of grade 3 injection site redness postdose 2 triggered predefined stopping rules.
  - This included 3 cases in the QS-21 study in the 50- to 64-year age cohort on the accelerated dosing schedule of Days 1, 8, and 30 (day regimen) and 7 cases in the Toxoid alone study in the 65-85 yr old cohort (Stage 2).
- Local reactions in both studies were more common among vaccine vs placebo recipients. Injection site pain predominated and was generally mild in severity. Systemic events were infrequent and generally mild to moderate in severity **(Figures 1–4)**.
  - Data shown in **Figure 3** and **Figure 4** include 6 confirmed e-diary data entry errors recorded as Severe and Grade 4.

### Adverse Events

- In both studies, reported AEs were generally consistent with illnesses and conditions expected in these age groups.
- QS-21 study:
  - AEs were reported by 50.0%–75.0% of subjects across all age cohorts, dosing regimens, and groups.
  - Related AEs were reported more frequently in the *C difficile* + QS-21 groups; those AEs reported >1 time within a given group included injection site reactions, fatigue, and nausea.
  - SAEs were reported by 0.0%–6.7% of subjects across the *C difficile* + QS-21 groups, but none were considered related to vaccination.
  - Four subjects across all groups were withdrawn from the study in connection with unrelated AEs that included basal cell carcinoma, gastroenteritis of presumed viral etiology, atrial fibrillation, and upper respiratory tract infection.
- Toxoid-alone study:
  - AEs were reported by 16.7%–50.0% of subjects across groups in both age cohorts.
  - Related AEs were more frequently reported in the active vaccine groups. Those reported >1 time within a given group were limited to various injection site reactions. The only related severe AEs were concerning injection site reactions.
  - SAEs were reported by 0.0%–16.7% of subjects across all groups; none were considered related to the investigational product. The only subject withdrawn from the study due to an AE was the subject who died of cardiac arrest (occurring on day 18 after dose 2; not considered related to the investigational product).

**Figure 1: Local Reactions and Systemic Events in QS-21 (50–64 y)**

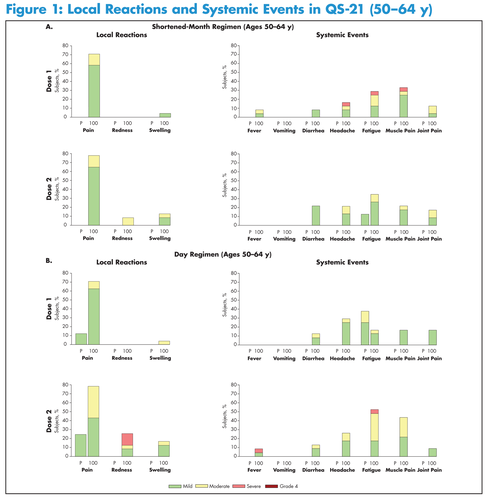



**Figure 2: Local Reactions and Systemic Events in QS-21 (65–85 y)**

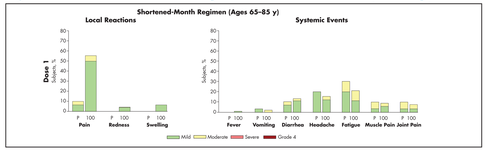
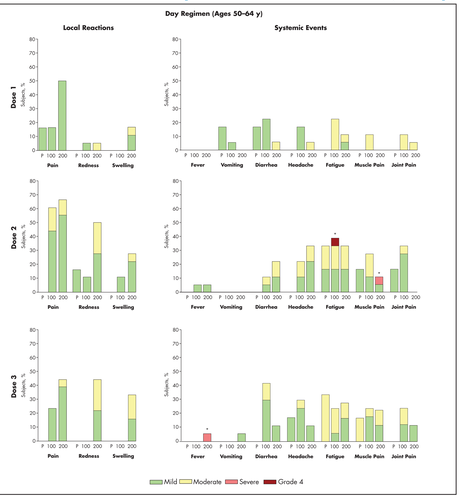
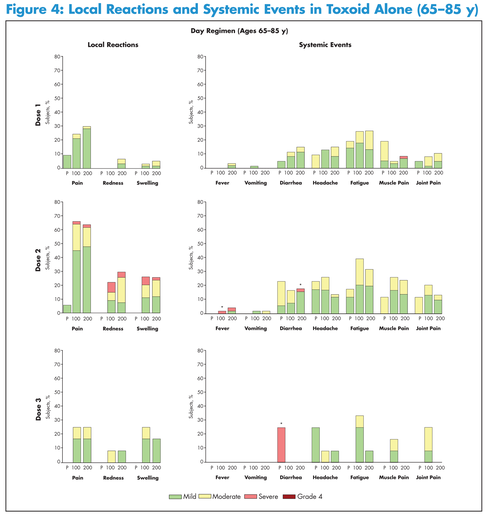



**Figure 3: Local Reactions and Systemic Events in Toxoid Alone (50–64 y)**




*Includes a confirmed e-diary data entry error.

**Figure 4: Local Reactions and Systemic Events in Toxoid Alone (65–85 y)**




*Includes a confirmed e-diary data entry error.

### Immunogenicity

- In both studies, geometric mean concentrations (GMCs) increased after vaccination in the active vaccine group(s) and remained elevated throughout the immunogenicity follow-up period **(Figures 5–6)**.
- The toxoid-alone study had more extensive immunogenicity data available compared with the QS-21 study; a number of subjects in the toxoid-alone study received all 3 doses, and immune responses were evaluated through 12 months postdose 3.

**Figure 5: GMCs in QS-21**

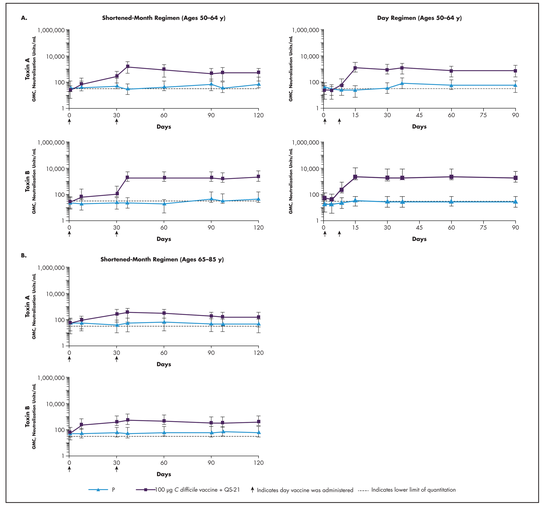
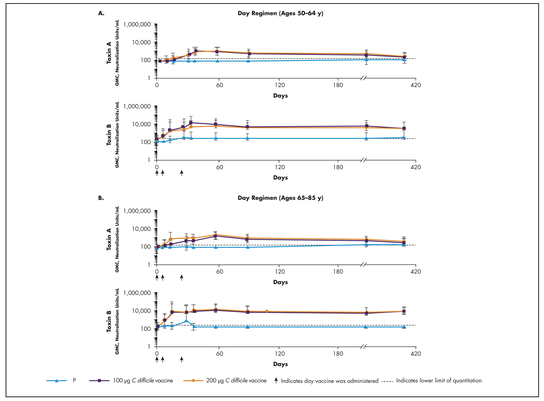



**Figure 6: GMCs in Toxoid Alone**




## CONCLUSION

- **The two *C difficile* vaccine formulations (adjuvanted QS-21 and toxoid-alone) demonstrated robust immunogenicity. However, both studies stopped early due to grade 3 injection site redness postdose 2 of the day (Days 1, 8, 30) regimen; neither formulation progressed to later-stage development.**
- **Instead, an aluminum hydroxide–containing formulation of the vaccine candidate administered at 0, 1, and 6 months, which was safe and immunogenic in phase 1 and 2 studies, advanced to phase 3 studies.**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## DISCLOSURES

All authors are employees of Pfizer Inc and may hold stock or stock options.


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