A PHASE II STUDY OF THE SAFETY AND IMMUNOGENICITY OF DIFFERENT VACCINATION SCHEDULES OF A CANDIDATE CLOSTRIDIUM DIFFICILE TOXOID VACCINE: VACCINATION SCHEDULE SELECTION FOR PHASE III

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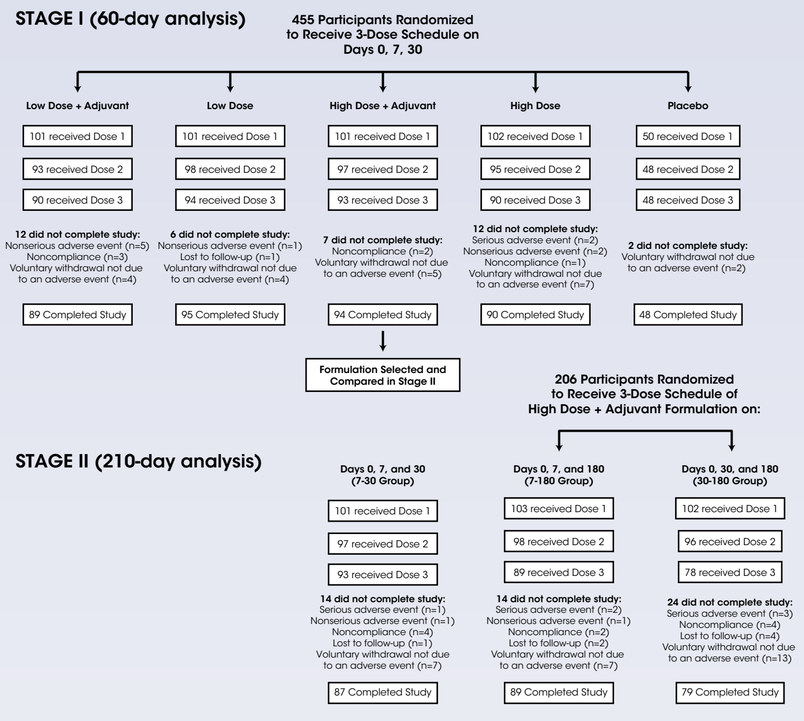
INTRODUCTION

- *Clostridium difficile* is a ubiquitous, gram-positive, spore-forming anaerobic pathogen causing disease ranging from mild self-limited diarrhea to life-threatening pseudomembranous colitis
- *C. difficile* infection (CDI) is mediated by 2 toxins, A and B, which damage intestinal epithelial cells and cause the clinical illness
- Given the global burden of disease and economic impact of this pathogen, CDI is an important target for prevention through vaccination
- Sanofi Pasteur is developing a vaccine against CDI
- The primary study objectives were to describe the safety profile of participants in each of the study groups and to describe the immune responses elicited by toxoid A and toxoid B of participants in each of the study groups
- ClinicalTrials.gov Accession #: NCT01230957
- Source of funding: Sanofi Pasteur

METHODS

- Trial Design: A phase II, randomized, placebo-controlled, modified double-blind, dose-ranging, multi-center, 2-stage trial (Stage 1 to select a preferred formulation; Stage 2 to select a preferred vaccine schedule)
  - The schedule-selection Stage II results are reported here
- Participants: Adults aged 40 to 75 years at risk for C. difficile infection due to:
  - Impending hospitalization ≤60 days before study entry
  - Current or impending residence in a long-term care facility or rehabilitation facility ≤60 days before study entry
- Setting and Locations: 39 clinical research cites in the United States
- Interventions: Participants received a 3-dose schedule of the ACAM-CDIFF vaccine formulation selected in Stage I, namely High Dose+Adjuvant
  - 3 different 3-dose schedules were compared
    - 7-30 Group – received doses on Days 0, 7 and 30 (the High Dose + Adjuvant Arm from Stage 1)
    - 7-180 Group – received doses on Days 0, 7, and 180 (recruited separately as a comparator)
    - 30-180 Group – received doses on Days 0, 30, and 180 (recruited separately as a comparator)
- Primary Outcomes
  - Safety:
    - Solicited reactions reported for 6 days postvaccination
    - Unsolicited adverse events (AEs) for 30 days postvaccination
    - Biological safety parameters
    - Serious adverse events (SAEs) throughout the study
    - Safety follow-up 6 months after administration of the last vaccine dose (Day 210 or Day 360)
  - Immunogenicity:
    - Blood samples obtained on Days 0, 14, 30, 60, 180, and 210
    - Assessed for anti-toxin A and B IgG concentrations and anti-toxin A and B neutralizing activity (TNA)
    - Conducted at Sanofi Pasteur Global Clinical Immunology laboratories in Swiftwater, PA, USA.
- Randomization/Blinding:
  - Centralized, age-stratified, computer-generated system allocated participants 1:1 to the 7-180 Group and the 30-180 Group
    - The group size was designed to be of equivalent size to the 7-30 Group
  - Participants, investigators, study staff collecting safety data, and laboratory personnel analyzing blood samples were blinded to study assignments
- Statistical Methods: The percentage of participants reporting
  - Unsolicited AEs ≤30 minutes postvaccination
  - Solicited injection site reactions (pain, erythema, and swelling) and systemic reactions (fever, headache, malaise, myalgia, and arthralgia) ≤6 days postvaccination (Day 0 to Day 6) by intensity, time to onset, number of days of occurrence, and action taken
  - Unsolicited AEs ≤30 days postvaccination by MedDRA system organ class and preferred term
  - SAEs throughout the trial by MedDRA system organ class and preferred term, outcome, seriousness, outcome, and relation to vaccination
  - Exact 2-sided 95% CIs for the proportions were computed by the Clopper-Pearson method
  - The sample size was not hypothesis-driven
    - The sample size could detect a minimum geometric mean fold ratio of 3.3 between vaccine and placebo groups, assuming 16% drop out rate
    - The sample size had a 95% probability of observing an adverse event (AE) at an incidence rate of 3% in the non-placebo arms
- Ranking/Selection Analysis:
  - Ranking/selection analysis on immunogenicity outcomes determined the best formulation for Stage II
  - The most immunogenic study group was selected by bootstrapping
  - A separate ranking was applied for each toxin, as well as a composite (toxin A and B) at each bootstrap replicate based on GMC
  - ELISA IgG composite with the highest ranking was the primary discriminator.
    - TNA results were considered supportive information

Figure 1. CONSORT Participant Disposition and Study Scheme



Participant Demographics

	7-30 Group (N=101)	7-180 Group (N=103)	30-180 Group (N=102)
Women, n (%)	57 (56.4)	59 (57.3)	66 (64.7)
Mean age in years (SD)	62.6 (8.6)	62.4 (9.0)	62.2 (10.3)
Ethnicity, n (%)			
White	94 (93.1)	97 (94.2)	94 (92.2)
Black	2 (2.0)	4 (3.9)	4 (3.9)
Hispanic	4 (4.0)	1 (1.0)	3 (2.9)
Native Hawaiian/Pacific Islands	1 (2.0)	0 (0)	0 (0)

Safety Overview

% With ≥1 Adverse Event (95% CI)	7-30 Group (N=101)	7-180 Group (N=103)	30-180 Group (N=102)
Immediate unsolicited AE	2.0 (0.2; 7.0)	1.0 (0; 5.3)	1.0 (0; 5.3)
Immediate unsolicited AR	1.0 (0; 5.4)	1.0 (0; 5.3)	1.0 (0; 5.3)
Solicited reaction	75.2 (65.7; 83.3)	82.2 (73.3; 89.1)	83.0 (74.2; 89.8)
Solicited injection site reaction	54.5 (44.2; 64.4)	70.3 (60.4; 79.0)	66.0 (55.8; 75.2)
Solicited systemic reaction	58.4 (48.2; 68.1)	64.4 (54.2; 73.6)	62.0 (51.7; 71.5)
Unsolicited AE	74.3 (64.6; 82.4)	66.0 (56.0; 75.1)	75.5 (66.0; 83.5)
Unsolicited AR	18.8 (11.7; 27.8)	20.4 (13.1; 29.5)	20.6 (13.2; 29.7)
Unsolicited non-serious AE	71.3 (61.4; 79.9)	66.0 (56.0; 75.1)	74.5 (64.9; 82.6)
Unsolicited non-serious AR	18.8 (11.7; 27.8)	20.4 (13.1; 29.5)	20.6 (13.2; 29.7)
Unsolicited non-serious injection site AR	15.8 (9.3; 24.4)	17.5 (10.7; 26.2)	15.7 (9.2; 24.2)
Unsolicited non-serious systemic AE	65.3 (55.2; 74.5)	59.2 (49.1; 68.8)	69.6 (59.7; 78.3)
Unsolicited non-serious systemic AR	4.0 (1.1; 9.8)	3.9 (1.1; 9.6)	8.8 (4.1; 16.1)
AE leading to study discontinuation	1.0 (0; 5.4)	1.0 (0; 5.3)	1.0 (0; 5.3)
SAEs to Day 60	15.8 (9.3; 24.4)	12.6 (6.9; 20.6)	17.6 (10.8; 26.4)
Deaths to Day 60	1.0 (0; 5.4)	1.9 (0.2; 6.8)	1.0 (0; 5.3)

- None of the SAEs were vaccination-related

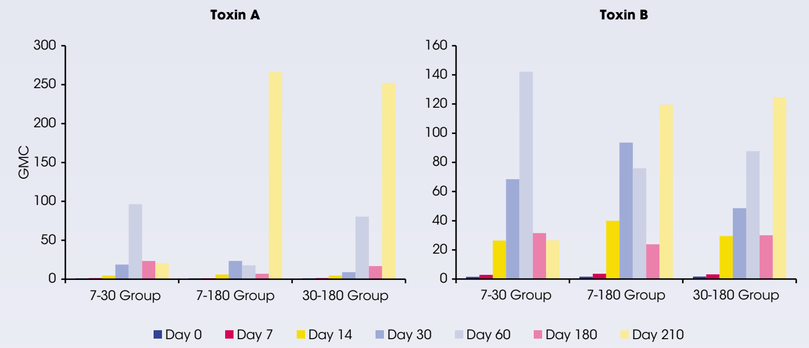
Summary of Solicited Reactions After Any Injection

% With ≥1 Adverse Event (95% CI)	7-30 Group (N=101)	7-180 Group (N=103)	30-180 Group (N=102)
Solicited reactions	75.2 (65.7; 83.3)	82.2 (73.3; 89.1)	83.0 (74.2; 89.8)
Injection site reactions	54.5 (44.2; 64.4)	70.3 (60.4; 79.0)	66.0 (55.8; 75.2)
Injection site pain	52.5 (42.3; 62.5)	68.3 (58.3; 77.2)	65.0 (54.8; 74.3)
Injection site erythema	6.9 (2.8; 13.8)	11.9 (6.3; 19.8)	5.0 (1.6; 11.3)
Injection site swelling	5.0 (1.6; 11.2)	9.9 (4.9; 17.5)	8.0 (3.5; 15.2)
Systemic reaction	58.4 (48.2; 68.1)	64.4 (54.2; 73.6)	62.0 (51.7; 71.5)
Fever	1.0 (0; 5.4)	5.9 (2.2; 12.5)	3.0 (0.6; 8.5)
Headache	31.7 (22.8; 41.7)	35.6 (26.4; 45.8)	32.0 (23.0; 42.1)
Malaise	33.7 (24.6; 43.8)	30.7 (21.9; 40.7)	29.0 (20.4; 38.9)
Myalgia	42.6 (32.8; 52.8)	38.6 (29.1; 48.8)	45.0 (35.0; 55.3)
Arthralgia	23.8 (15.9; 33.3)	26.7 (18.4; 36.5)	30.0 (21.2; 40.0)

SAFETY CONCLUSIONS

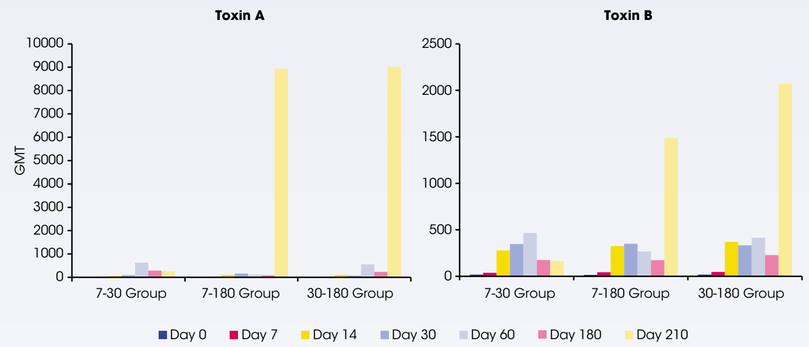
- The solicited ARs and unsolicited AEs were generally Grade 1 in intensity, of short duration, did not lead to study discontinuations, and were not considered clinically significant

Summary of ELISA Geometric Mean Concentrations (EU/mL [95% CI])



- The vaccine elicited responses to both Toxin A and Toxin B
- Peak responses were noted at Day 60, 30 days after the last dose of study vaccine for the 7-30 Group
- There is also a strong anamnestic response in the 7-180 Group and the 30-180 Group after a decline in immune response post-Dose 2

Summary of TNA Geometric Mean Titers (1/dil [95% CI])



Percentage of participants with ≥4-fold rise ELISA seroconversion, by study day (Per-Protocol Analysis Set)

Study Day	7-30 Group (N=66)	7-180 Group (N=61)	30-180 Group (N=57)
30	46.2	62.3	42.1
60	90.9	60.7	84.2
180	68.2	37.7	54.7

CONCLUSIONS

- The solicited ARs and unsolicited AEs were generally Grade 1 in intensity, of short duration, did not lead to study discontinuations, and were not considered clinically significant
  - Reported SAEs were not related to vaccination
- There were more solicited injection site and systemic reactions in the 7-180 and 30-180 Groups; however, the tolerability profile of all regimes was deemed acceptable
- The 0-7-30 day schedule (7-30 Group) resulted in a preferred immune response profile for the vaccine targeted population
- In groups receiving a dose at day 180, we observed evidence for anamnestic boosting, indicating the potential to sustain immunological memory
- The 0–7–30 schedule was selected for further study in Phase III

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