A PHASE II STUDY OF THE SAFETY AND IMMUNOGENICITY OF DIFFERENT FORMULATIONS OF A CANDIDATE CLOSTRIDIUM DIFFICILE TOXOID VACCINE: DOSE AND FORMULATION SELECTION FOR PHASE III

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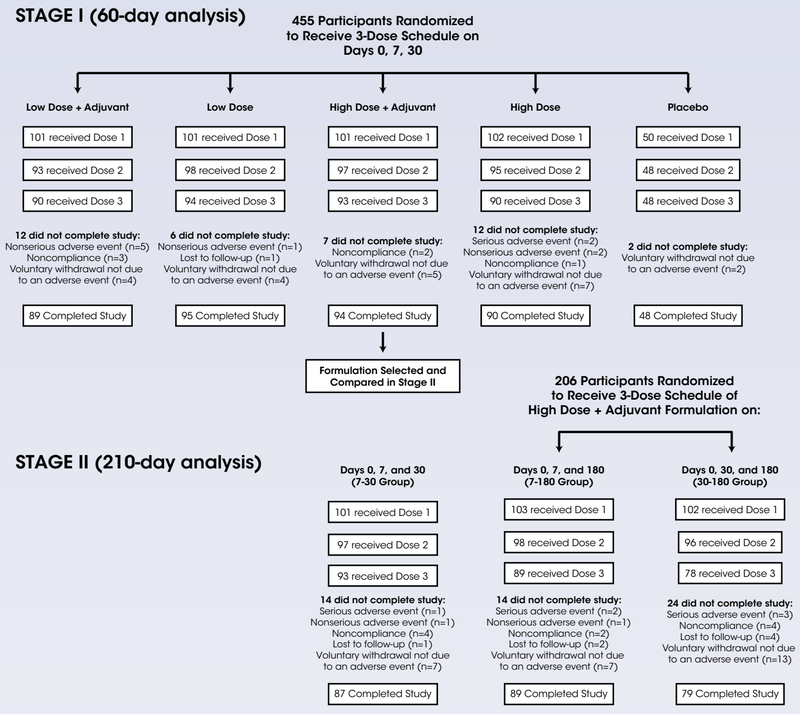
INTRODUCTION

- *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 Toxin A and Toxin B, which damage intestinal epithelial cells and cause the clinical illness
- Given the global disease burden and economic impact, CDI is a target for prevention through vaccination
- Sanofi Pasteur performed a clinical study assessing a CDI vaccine with 2 objectives
  - Describe the safety profile of study participants
  - Describe participant immune responses elicited by toxoid A and toxoid B
- WHO Universal Trial Number (UTN): U1111-1114-3917
- 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 dose-finding Stage I 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 were assigned to Study Groups and received 3 doses of 1 of 4 different formulations of ACAM-CDIFF vaccine or placebo on Day 0, 7, and 30
  - Low Dose + Adjuvant
  - Low Dose
  - High Dose + Adjuvant
  - High Dose
  - Saline Placebo
- Primary Outcomes
  - Safety:
    - Solicited reactions reported for 6 days postvaccination
    - Unsolicited adverse events (AEs) 30 days postvaccination
    - Serious adverse events (SAEs) throughout the trial
    - For all participants, safety follow-up continued 6 months post-Dose 3 (Day 210)
  - Immunogenicity:
    - Blood samples obtained on Day 0, 14, 30, and 60
    - Assessed for anti-toxin A and B IgG concentrations and anti-toxin A and B neutralizing activity (TNA)
    - Conducted at the Sanofi Pasteur Global Clinical Immunology laboratories in Swiftwater, PA, USA.
- Randomization/Blinding:
  - Centralized, age-stratified, computer-generated system allocated participants in a 2:2:2:2:1 ratio.
  - 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
  - The formulation eliciting the best immune response in elderly subjects was also a consideration

Figure 1. CONSORT Participant Disposition and Study Scheme



Participant Demographics

	Low Dose+Adj (N=100)	Low Dose (N=102)	High Dose+Adj (N=101)	High Dose (N=102)	Placebo (N=50)
Women, n (%)	45 (45.0)	57 (55.9)	57 (56.4)	51 (50.0)	30 (60.0)
Mean age in years (SD)	61.8 (8.8)	62.1 (9.7)	62.6 (8.6)	62.3 (9.4)	62.1 (8.2)
Ethnicity, n (%)					
White	93 (93.0)	85 (83.3)	94 (93.1)	95 (93.1)	42 (84.0)
Black	3 (3.0)	13 (12.7)	2 (2.0)	3 (2.9)	4 (8.0)
Hispanic	3 (3.0)	4 (3.9)	4 (4.0)	4 (3.9)	2 (4.0)
Native American/Alaskan	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.0)
Native Hawaiian/Pacific Islands	0 (0)	0 (0)	1 (2.0)	0 (0)	0 (0)
Other	1 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)

Safety

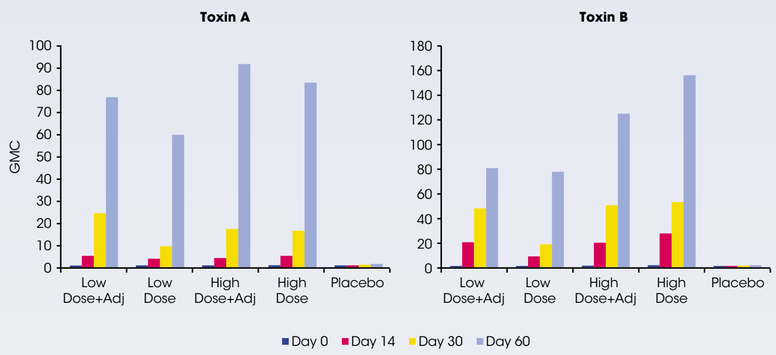
% With ≥1 Adverse Event (95% CI)	Low Dose+Adj (N=100)	Low Dose (N=102)	High Dose+Adj (N=101)	High Dose (N=102)	Placebo (N=50)
Immediate unsolicited AE	1.0 (0; 5.4)	2.9 (0.6; 8.4)	2.0 (0.2; 7.0)	1.0 (0.0; 5.3)	2.0 (0.1; 10.6)
Immediate unsolicited AR	1.0 (0; 5.4)	2.0 (0.2; 6.9)	1.0 (0; 5.4)	0 (0; 3.6)	0 (0; 7.1)
Solicited reaction	70.1 (60.0; 79.0)	69.7 (59.6; 78.5)	75.2 (65.7; 83.3)	69.8 (59.6; 78.7)	43.8 (29.5; 58.8)
Solicited injection site reaction	53.6 (43.2; 63.8)	43.4 (33.5; 53.8)	54.5 (44.2; 64.4)	58.3 (47.8; 68.3)	25.0 (13.6; 39.6)
Solicited systemic reaction	58.8 (48.3; 68.7)	57.6 (47.2; 67.5)	58.4 (48.2; 68.1)	52.1 (41.6; 62.4)	37.5 (24.0; 52.6)
Unsolicited AE	76.0 (66.4; 84.0)	58.8 (48.6; 68.5)	73.3 (63.5; 81.6)	62.7 (52.6; 72.1)	56.0 (41.3; 70.0)
Unsolicited AR	18.0 (11.0; 26.9)	9.8 (4.8; 17.3)	18.8 (11.7; 27.8)	11.8 (6.2; 19.6)	0 (0; 7.1)
Unsolicited non-serious AE	75.0 (65.3; 83.1)	55.9 (45.7; 65.7)	70.3 (60.4; 79.0)	57.8 (47.7; 67.6)	52.0 (37.4; 66.3)
Unsolicited non-serious AR	18.0 (11.0; 26.9)	9.8 (4.8; 17.3)	18.8 (11.7; 27.8)	11.8 (6.2; 19.6)	0 (0; 7.1)
Unsolicited non-serious injection site AR	5.0 (8.6; 23.5)	6.9 (2.8; 13.6)	15.8 (9.3; 24.4)	9.8 (4.8; 17.3)	0 (0; 7.1)
Unsolicited non-serious systemic AE	71.0 (61.1; 79.6)	53.9 (43.8; 63.8)	63.4 (53.2; 72.7)	54.9 (44.7; 64.8)	52.0 (37.4; 66.3)
Unsolicited non-serious systemic AR	15.0 (1.6; 11.3)	2.9 (0.6; 8.4)	4.0 (1.1; 9.8)	2.0 (0.2; 6.9)	0 (0; 7.1)
AE leading to study discontinuation	5.0 (1.6; 11.3)	1.0 (0; 5.3)	1.0 (0; 5.4)	3.9 (1.1; 9.7)	0 (0; 7.1)
SAEs to Day 60	9.0 (4.2; 16.4)	13.7 (7.7; 22.0)	7.9 (3.5; 15.0)	9.8 (4.8; 17.3)	8.0 (2.2; 19.2)
Deaths to Day 60	0 (0; 3.6)	0 (0; 3.6)	0 (0.0; 3.6)	0 (0; 3.6)	0 (0.0; 7.1)

- There were no vaccination-related SAEs reported
- 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
- There were more solicited injection site and systemic reactions in the vaccine treatment groups

Solicited Reactions

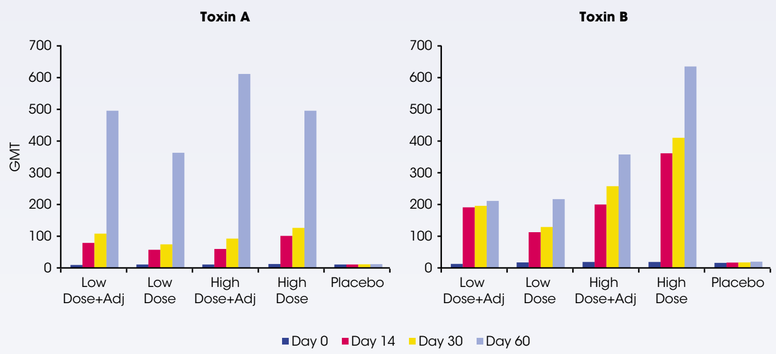
% With ≥1 Adverse Event (95% CI)	Low Dose+Adj (N=100)	Low Dose (N=102)	High Dose+Adj (N=101)	High Dose (N=102)	Placebo (N=50)
All Solicited reactions	70.1 (60.0; 79.0)	69.7 (59.6; 78.5)	75.2 (65.7; 83.3)	69.8 (59.6; 78.7)	43.8 (29.5; 58.8)
Injection site reactions	53.6 (43.2; 63.8)	43.4 (33.5; 53.8)	54.5 (44.2; 64.4)	58.3 (47.8; 68.3)	25.0 (13.6; 39.6)
Pain	52.6 (42.2; 62.8)	42.4 (32.5; 52.8)	52.5 (42.3; 62.5)	57.3 (46.8; 67.3)	25.0 (13.6; 39.6)
Erythema	5.2 (1.7; 11.6)	3.0 (0.6; 8.6)	6.9 (2.8; 13.8	10.4 (5.1; 18.3)	0 (0; 7.4)
Swelling	6.2 (2.3; 13.0)	1.0 (0; 5.5)	5.0 (1.6; 11.2)	4.2 (1.1; 10.3)	0 (0; 7.4)
Systemic reactions	58.8 (48.3; 68.7)	57.6 (47.2; 67.5)	58.4 (48.2; 68.1)	52.1 (41.6; 62.4)	37.5 (24.0; 52.6)
Fever	5.3 (1.7; 11.9)	6.1 (2.3; 12.7)	1.0 (0; 5.4)	0 (0; 3.8)	0 (0; 7.4)
Headache	35.4 (25.9; 45.8)	27.3 (18.8; 37.1)	31.7 (22.8; 41.7)	30.2 (21.3; 40.4)	18.8 (8.9; 32.6)
Malaise	32.0 (22.9; 42.2)	32.3 (23.3; 42.5)	33.7 (24.6; 43.8)	31.3 (22.2; 41.5)	20.8 (10.5; 35.0)
Myalgia	37.1 (27.5; 47.5)	33.3 (24.2; 43.5)	42.6 (32.8; 52.8)	34.4 (25.0; 44.8)	20.8 (10.5; 35.0)
Arthralgia	27.8 (19.2; 37.9)	20.2 (12.8; 29.5)	23.8 (15.9; 33.3)	24.0 (15.8; 33.7)	12.5 (4.7; 25.2)

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

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	Low Dose+Adj (N=70)	Low Dose (N=68)	High Dose+Adj (N=73)	High Dose (N=73)	Placebo (N=38)
14	29	29.4	23.6	25.4	0
30	62.9	38.2	44.4	50.7	2.6
60	85.5	82.4	90.4	87.3	7.9

CONCLUSIONS

- Overall, the tolerability profiles of all doses were acceptable
  - Reported SAEs were not related to vaccination
  - Non-serious AEs did not lead to study discontinuation and were not vaccination-related
- Immune responses increased in all treatment groups with each dose through Day 60
- The composite ELISA ranking analysis, supported by ranking analysis for older participants (65 to 75 years), determined that the High Dose + Adjuvant formulation more immunogenic than the other formulations
- The High Dose + Adjuvant formulation was selected for further study in Stage II of the protocol

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