



SANOFI PASTEUR INVESTIGATIONAL CLOSTRIDIUM DIFFICILE VACCINE PHASE II DATA

OVERVIEW

Sanofi Pasteur is developing a novel, investigational vaccine for the prevention of ***Clostridium difficile*** (*C. difficile*) infection (CDI). Vaccination could be an efficacious, cost-effective and important public health measure to help protect individuals from *C. difficile* bacteria, which is emerging as a leading cause of healthcare-associated infections (HAIs).¹ If proven to prevent CDI, the Sanofi Pasteur vaccine would be the first preventative vaccine of its kind against the symptoms of this infection.

The Phase II trial (H-030-012) met its primary objectives, reactions were generally mild and of short duration, and the candidate vaccine generated an immune response against *C. difficile* toxins A and B. The resulting data led to the selection of a vaccine formulation and dosing schedule for the Phase III global efficacy program, ***Cdiffense***[™], which is currently underway with plans to include up to ~200 sites across 20+ countries.

C. difficile toxins A and B are primarily responsible for CDI, which can cause potentially life-threatening gut inflammation and diarrhea.¹ Antibody increases to these toxins were observed across different dosing groups and schedules in a variety of ages throughout the Phase II trial.

RESULTS

Based on the study results, a high-dose plus adjuvant vaccine formulation administered on days 0, 7 and 30 was selected for further evaluation in the Phase III program.

Immunogenic effects were measured using both Enzyme Linked Immunosorbent Assay (ELISA), which assesses anti-toxin A and B immunoglobulin G (IgG) concentrations, and Toxin Neutralization Activity (TNA), which measures anti-toxin A and B neutralizing activity. Analysis was conducted on days 0, 7, 14, 30, 60, 180 and 210.

The high-dose plus adjuvant vaccine formulation demonstrated the best immune response over a 30-, 60- and 180-day period, particularly in volunteers aged 65-75 years. Composite ELISA ranking analysis also determined that the selected candidate generated the greatest immune response over a 60-day period and showed four-fold increases in the development of detectable antibodies for both toxins A and B. Peak responses were noted at day 60 (30 days after the last dose of vaccine).

The safety profile of all vaccine doses was deemed acceptable throughout the Phase II study. Reactions were monitored until day 210 and were generally Grade 1 (classified as mild), of short duration, did not lead to study discontinuations and were not considered clinically significant.



DESIGN AND INCLUSION CRITERIA

The Phase II study was a randomized, multi-center trial split into two stages and conducted at 39 sites across the United States. The first stage was placebo-controlled, modified double-blind and designed for dose and formulation selection among 455 volunteers. The second stage was designed for schedule selection, comparing the dose and formulation prioritized in Stage 1 with two alternate dosing schedules among 206 additional volunteers.

The Phase II trial evaluated 661 male and female volunteers, aged 40 to 75, who met the following criteria:

- Were at risk of developing CDI due to either –
 - a) Impending elective surgery or hospitalization within 60 days of enrollment
 - b) Current or impending residence in a long-term care facility or rehabilitation facility
- If a female of childbearing age, actively protected against pregnancy four weeks prior to starting the trial, during the study and/or four weeks after the last vaccination
- Provided informed consent and were able to attend all scheduled visits and follow trial procedures

DOSING

Stage 1

Participants in Stage 1 were randomized into one of five study groups: high-dose or low-dose vaccine either with or without adjuvant, or placebo. Each vaccine formulation or placebo was administered on days 0, 7 and 30.

- **Group 1, N=100:** Low dose plus adjuvant
- **Group 2, N=102:** Low dose
- **Group 3, N=101:** High dose plus adjuvant
- **Group 4, N=102:** High dose
- **Group 5, N=50:** Placebo

Stage 2

The high-dose vaccine plus adjuvant formulation (Group 3 from Stage 1) was selected for further testing in Stage 2 and was evaluated across three administration schedules:

- **Group 3, N=101:** Days 0, 7 and 30 (*data applied from Stage 1*)
- **Group 6, N=103:** Days 0, 7 and 180
- **Group 7, N=102:** Days 0, 30 and 180

¹ Lessa F, Gould C, and McDonald LC. Current Status of Clostridium difficile Infection Epidemiology. Clinical Infectious Diseases. August 2012; 55(Suppl 2): S65-S70. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3388017/?report=classic>.

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