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Vaccine development

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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Objectives: Sanofi Pasteur is developing a toxoid vaccine for the prevention of first occurrence *Clostridium difficile* infection (CDI) in at-risk individuals. The data reported here constitute the first stage of a two-stage Phase II safety and immunogenicity study, with the objective of selecting the most appropriate dose and formulation for use in Phase III clinical development. (The selection of the vaccination schedule comprised a second stage of the same study, and is presented in an accompanying abstract.)

Methods: Phase II, randomized, placebo-controlled, double-blind, multi-center study in adults aged 40-75 years and at risk of CDI (defined as those with impending hospitalization or residence in a long-term care facility). Subjects were randomized to receive either a low dose of antigen with (Group 1, N=101) or without (Group 2, N=101) adjuvant, or high dose of antigen with (Group 3, N=101) or without (Group 4, N=102) adjuvant, or placebo (Group 5, N=50). The vaccination schedule was Day 0, 7, and 30. Post-vaccination solicited and unsolicited adverse events were collected after each dose, and serious adverse events (SAEs) were monitored to Day 210. For the selection of the dose and formulation, IgG specific for *C. difficile* toxins A and B were assessed by ELISA and also for toxin neutralization activity on Days 0, 14, 30, and 60; the results were assessed using decision tree analysis, bootstrap composite analysis, geometric mean concentrations, seroconversion, and reverse cumulative distribution curves. The selection was made on data to Day 60 in order to proceed to the second stage of the study (schedule selection), and additional timepoints (Days 180 and 210) were subsequently assessed. All analyses were descriptive.

Results: Demographic characteristics were similar in each group. There were no safety concerns in any group: the incidence of Grade 3 solicited and unsolicited reactions was similar in each treatment group and no SAE was considered to be related to vaccination. For the immune response, a treatment effect trend was noted in all vaccine groups compared to placebo, with robust responses that continued to increase at Day 60. The high dose + adjuvant group (Group 3) demonstrated the best immune response, particularly in those aged 65-75 years, an age group considered to be a major portion of the target population. Analysis of the immune response data at Days 180 and 210 supported the dose and formulation selected at Day 60.
Conclusion: The candidate vaccine was well tolerated and immunogenic for toxins A and B. In the absence of any safety concern, and given the superior immune response, the high dose + adjuvant formulation was selected for further development of this novel *C. difficile* toxoid vaccine.