WHOLE VIRUS ALUM-ADJUVANTED PANDEMIC VACCINE: SAFETY AND IMMUNOGENICITY DATA ON A VACCINE FORMULATED WITH H5N1

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Background: In the case of an influenza pandemic, most of the population will be naïve to the pandemic viral strain therefore two doses of vaccine are likely to be required for protection. In order to reduce the time required for vaccine production while simultaneously increasing vaccine supply capacity, there are two approaches: an antigen-sparing strategy using adjuvanted formulations, and the use of whole virus antigen instead of the more commonly used split or subunit antigens. Previous studies have combined these approaches using H9N2 or H2N2 strains in adjuvanted whole virus prototype vaccine formulations. With the H5N1 avian influenza strain emerging as an important pandemic strain, a clinical trial was performed evaluating this approach in a whole virus Alum-adjuvanted pandemic candidate vaccine formulated with H5N1.

Aims: To evaluate in healthy adults (18 to 60 years) (1) the safety and reactogenicity and (2) the immune responses of various antigen doses of a GlaxoSmithKline Biologicals' candidate H5N1 whole virus Alum-adjuvanted/non-adjuvanted pandemic influenza vaccine.

Methods: 400 adults (8 parallel groups) were enrolled in a phase I, partially-blind, multi-center randomized study (106378/NCT00309647) and were administered Alum-adjuvanted or non-adjuvanted H5N1 A/Vietnam/1194/04 whole virus pandemic candidate vaccine containing 3.8µg, 7.5µg, 15µg or 27µg hemagglutinin (HA). Two doses were administered intramuscularly on day 0 and day 21. On days 0, 21 and 42, blood samples were collected for humoral immune response analysis. Target guidelines set by regulatory agencies (European Authorities, EMEA) for the annual registration of seasonal influenza vaccines and expected for pandemic influenza vaccines were used. Diary cards were filled by subjects to record solicited local and systemic symptoms (7 days) as well as unsolicited adverse events (51 days). Serious adverse events (SAEs) were recorded throughout the study period.

Results: After the second dose, seroconversion (SC) and seroconversion factor (SCF) thresholds required by EMEA (SC≥40%, SCF≥2.5) were achieved in all whole virus H5N1 vaccine groups. The seroprotection (SP) threshold required by EMEA (SP≥70%) was reached only in the vaccine groups receiving antigen contents of 15µg and 27µg HA. This was irrespective of the presence of Alum as adjuvant. However, after two doses, the 3.8µg HA Alum-adjuvanted formulation met both the SC rate and SCF criteria from EMEA but was just below the SP criterion (69.4% [95%CI: 54.6-81.7]). In the groups with low antigen contents (3.8µg and 7.5µg HA), higher SCF, SC and SP rates were observed using Alum-adjuvanted formulations compared to non-adjuvanted formulations.

The most frequently reported local symptom was pain and was similar for all groups. As reported with other influenza vaccines, the most frequent general symptoms were headaches and myalgia in both Alum-adjuvanted and non-adjuvanted groups. The safety profile of all groups was considered clinically acceptable. No SAE related to study vaccine was reported.

Conclusion: These results suggest that an Alum-adjuvanted whole virus vaccine even with low HA content (3.8µg) can raise a strong antibody response following administration of two vaccine doses to a naïve adult population. However, to meet EMEA’s criteria for seroprotection two doses containing at least 15µg of H5N1 whole virus antigen adjuvanted or not with Alum are needed.