SAFETY AND IMMUNOGENICITY OF AN AS ADJUVANTED H5N1 PREPANDEMIC INFLUENZA VACCINE: A PHASE III STUDY IN A LARGE POPULATION OF ASIAN ADULTS.

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Background: The use of a prepandemic influenza vaccine, either before or just after a pandemic outbreak, is considered to be one of the most effective measures to reduce the incidence of the infection and consequently its morbidity and mortality. A dose ranging analysis has demonstrated that the GlaxoSmithKline Biologicals’ prepandemic influenza split virus candidate vaccine adjuvanted with the novel proprietary Adjuvant System (AS) was clinically acceptable and induced - even with a formulation containing only 3.8µg haemagglutinin (HA) antigen - a high level of haemagglutination inhibition and neutralizing antibodies directed against the H5N1 A/Vietnam 1194/04 (clade 1) vaccine strain (Leroux-Roels et al., The Lancet 370:580-9, 2007). In the present study, we assessed in a larger cohort of Asian adults the safety of the AS adjuvanted formulation containing 3.8µg of HA antigens and the immunogenic response against clade 1 and clade 2 strains.

Methods: This phase III lot-to-lot consistency study (109630/NCT:00449670) was conducted in 4 Asian countries, in adults aged 18-60 years and vaccinated 21 days apart with two doses of a H5N1 split virus influenza vaccine containing 3.8µg HA adjuvanted (N=961) or not (N=245) with a proprietary oil-in-water emulsion based Adjuvant System. At days 0, 21 and 42, blood samples were collected. To assess the immunogenicity of the candidate vaccine, the antibodies inhibiting haemagglutination (HI) and the neutralizing (NT) antibodies against both the vaccine strain A/Vietnam/1194/2004 (clade 1) and the A/Indonesia/05/2005 strain (clade 2) were measured. Seroprotection rates for HI as well as seroconversion rates for NT were calculated. An HI titer >1:40 was considered to be seroprotective. The conventional 4-fold increase in neutralizing titer was used to assess seroconversion. Results are expressed with 95% confidence intervals [95%CI]. Solicited local and general symptoms, unsolicited adverse events and serious adverse events (SAEs) were recorded.

Results: Using neutralization assay, results at day 42 from the AS-adjuvanted group showed seroconversion rates of 96.0% [93.0-98.0] and 91.4% [87.5-94.4] with neutralizing antibodies against the vaccine strain and against the Indonesia strain respectively, while in the non-adjuvanted vaccine group the seroconversion rates were 32.4% [21.8-44.5] and 5.6% [1.6-13.8]. Furthermore, despite a greater specificity towards the H-antigen of the HI assay, HI seroprotective titers against the A/Vietnam/1194/2004 and A/Indonesia05/2005 strain were observed at day 42, in 94.3 % [95% CI: 92.6-95.7] and in 50.2% [46.9-53.5] of subjects in the adjuvanted vaccine groups. In non-adjuvanted group, only 10.3% [6.7-14.9] and 0.4% [0.0-2.4] of the subjects presented HI seroprotective titers against the A/Vietnam and A/Indonesia strain. Although the adjuvanted formulation elicited a higher incidence of local and general symptoms than the non-adjuvanted vaccine, the reactogenicity profile was acceptable. The vaccine was associated with a favorable safety profile. No vaccine-related SAEs were reported. Lot-to-lot consistency was demonstrated.

Conclusion: In addition to allowing antigen dose-sparing, AS adjuvantation of inactivated split H5N1 vaccine promotes cross-clade immunity which is a pre-requisite for an effective pre-pandemic vaccination strategy.