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Immunogenicity and safety of an AS03-adjuvanted H5N1 pandemic influenza vaccine in Korean adults: A phase IV, randomized, open-label, controlled study

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ABSTRACT

Background: AS03-adjuvanted H5N1 pandemic influenza vaccines have been assessed in an extensive clinical development program conducted in North America, Europe, and Asia including children from 6 months of age, adults, and elderly adults. We evaluated AS03-H5N1 in Korean adults 18 through 60 years of age.

Methods: This Phase IV, randomized, study was conducted to assess the immunogenicity, reactogenicity, and safety of two doses (3.75 μg of hemagglutinin antigen) of A/Indonesia/5/2005 (H5N1) adjuvanted with AS03 given 21 days apart in Korean adults. Antibody responses were assessed using hemagglutination-inhibition (HI) assays against the vaccine strain and a vaccine-heterologous strain (A/Vietnam/1194/2004) 21 days after the second dose. A control group (safety) received a licensed seasonal inactivated trivalent influenza vaccine (TIV). Reactogenicity was assessed for 7 days after each vaccination, and unsolicited adverse events were assessed for 182 days following vaccination in both study groups (NCT01730378).

Results: AS03-H5N1 was immunogenic and elicited robust HI antibody responses with seroconversion rates of 100% for the vaccine strain and 69.1% for the heterologous strain ($N = 81$). HI antibody responses fulfilled the European licensure criteria for immunogenicity (primary endpoint). The incidence of local and systemic solicited adverse events (reactogenicity) was higher with AS03-H5N1 than TIV. There was no apparent difference in the rate of unsolicited adverse events in the AS03-H5N1 and TIV groups.

Conclusion: The results indicate that AS03-H5N1 vaccine is immunogenic with reactogenicity and safety findings that are consistent with the established profile of AS03-H5N1 vaccine.

1. Introduction

The World Health Organization (WHO) reported 667 human cases of avian-origin H5N1 infection from 2003 to July 2014, of which 393 were fatal [1]. The unpredictable nature of avian-origin H5N1 influenza should not be underestimated, and the development of vaccines against influenza viruses with pandemic-potential is a public health priority.

GSK Vaccines has produced H5N1 vaccines containing the A/Vietnam or A/Indonesia antigen formulated with the oil-in-water Adjuvant System, AS03. The AS03-adjuvanted H5N1 vaccines (AS03-H5N1) are manufactured at sites in Dresden, Germany,

Abbreviations: AEs, adverse events; CBER, US Center for Biologics Evaluation and Research; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GMT, geometric mean titer; HA, hemagglutinin antigen; HI, hemagglutination-inhibition; MAEs, medically-attended adverse events; MGI, mean geometric increase; pIMDs, potentially immune-mediated diseases; SAE, serious adverse event; SCR, seroconversion rate; SPR, seroprotection rates; WHO, World Health Organization.

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and Quebec, Canada, and are licensed in Europe and the US (*Prepandrix*™; *Adjupanrix*™; *Pumarix*™; Q-Pan H5N1 influenza vaccine) [2,3]. AS03-H5N1 vaccines have been assessed in large studies in North America, Europe, and Asia, including children from 6 months of age, adults, and elderly adults [4–10].

Pivotal Phase 3 trials in European and Asian adults showed that two doses of AS03-H5N1 (A/Vietnam/1194/2004) vaccine containing 3.75 μg of hemagglutinin antigen (HA) was more immunogenic than non-adjuvanted vaccines [4,8,11]. Across the clinical development program, AS03-H5N1 vaccines have been shown to elicit strong, durable, cross-clade immune responses [4–8]. Furthermore, a long-term extension phase of the Asian study conducted in Taiwan, Thailand, Singapore, and Hong Kong, suggested that vaccinated populations could potentially be protected for up to three years after vaccination, which is likely to far exceed the peak of pandemic transmission [12]. The results of the long-term study showed that AS03-H5N1 vaccine may be used according to flexible prime–boost vaccination schedules, with strong cross-clade anamnestic antibody responses observed after one dose of AS03-H5N1 heterologous booster vaccine given at 6, 12, or 36 months after priming with two doses of AS03-H5N1 vaccine [12].

This Phase IV, open-label study was conducted to assess the immunogenicity and safety of a two-dose schedule of AS03-H5N1 (A/Indonesia/5/2005) vaccine in Korean adults.

2. Methods

2.1. Design and objectives

This Phase IV, randomized, open-label study evaluated the immunogenicity, reactogenicity, and safety of a two-dose primary vaccination series of AS03-H5N1 (A/Indonesia/5/2005) vaccine in adults. A safety control group received one dose of seasonal inactivated trivalent influenza vaccine (TIV). The study was multi-center and conducted in the Republic of Korea.

The main immunogenicity objective (primary outcome) was to assess if two doses of AS03-H5N1 vaccine elicited hemagglutination-inhibition (HI)-based immune responses against the vaccine strain (A/Indonesia/5/2005) which fulfilled the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) licensure criteria for the approval of pandemic influenza vaccines [13]. The main safety objective (secondary outcome) was to evaluate solicited adverse events (AEs) and unsolicited AEs in the AS03-H5N1 group and the TIV control group.

Men and women were eligible for inclusion if they were 18 through 60 years of age at the first vaccination. Subjects were required to be in good general health with no acute illness and controlled chronic conditions. Subjects could not have received any seasonal or pandemic influenza vaccine within six months before study vaccination or during the study period. Women of child bearing potential were required to use reliable contraception.

All protocols and study documentation were approved by independent/local ethics committees in accordance with Good Clinical Practice, the Declaration of Helsinki, and regulatory requirements. (ClinicalTrials.gov NCT01730378). Subjects provided informed written consent.

2.2. Vaccines and randomization

The study vaccine was an H5N1 inactivated, split-virion recombinant influenza vaccine manufactured by GSK Vaccines in Dresden, Germany. Each dose of vaccine contained 3.75 μg HA of A/Indonesia/05/2005 adjuvanted with AS03, an oil-in-water emulsion based Adjuvant System containing 11.86 mg of α-tocopherol. The control vaccine was a licenced TIV for seasonal influenza (*Fluarix*™, GSK Vaccines) containing 15 μg of each HA that was recommended by the WHO for the 2012/13 influenza season in the Northern Hemisphere: A/Christchurch/16/10 (H1N1), A/Victoria/361/2011 (H3N2), and B/Hubei-Wujiagang/158/2009 (Yamagata lineage influenza B strain). The lot numbers were AFLSA340A (H5N1), AA03A209C (AS03), and AFLUA696A (*Fluarix*™).

Subjects were scheduled to receive two doses 21 days apart of AS03-H5N1 or one dose of TIV control vaccine, which were administered open-label in the deltoid muscle. Randomization was performed by GSK Vaccines (Rixensart, Belgium) using a blocking scheme developed in SAS® (Cary, NC, USA). Vaccines were allocated at each study site using an internet-based randomization system. Subjects were randomized 2:1 to receive AS03-H5N1 or control TIV, and a minimisation procedure was used to account for center, age strata (about 1:1 for 18–40 years and 41–60 years), and history of seasonal influenza vaccination and/or A(H1N1)pdm09 vaccine in preceding three seasons.

2.3. Immunogenicity assessments

Blood samples were taken for the evaluation of immune responses on Day 0, 21, and 42 in the AS03-H5N1 vaccine group (before and 21 days after each dose), and on Day 0 and 21 in the TIV group. In the AS03-H5N1 vaccines group, HI assays were performed using an established HI method, modified for equine rather than avian erythrocytes [14–16]. In the TIV group, HI assays against the three vaccine strains were measured using a validated method as previously described [17]. All serological testing was performed at a central GSK Vaccines laboratory.

The primary endpoint was the measurement of HI antibodies against A/Indonesia/5/2005 at Day 42 (21 days after the second vaccination) to evaluate whether two doses AS03-H5N1 vaccine elicited immune responses that fulfilled the CHMP licensure criteria for immunogenicity [13]. Secondary immunogenicity endpoints were to assess if two doses of vaccine fulfilled the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) licensure criteria for immunogenicity [18], and to assess HI antibody responses after one dose of AS03-H5N1 vaccine. Tertiary immunogenicity analyses were the assessment of Day 42 HI antibody responses against a vaccine-heterologous strain (A/Vietnam/1194/2004), and vaccine-homologous responses according to age (18–40 years or 41–60 years), and according to previous vaccination history (vaccinated or not vaccinated against seasonal or A(H1N1)pdm09 influenza during the previous three seasons). HI immune responses to the three strains in the TIV control vaccine were also assessed.

HI antibody parameters were Geometric Mean Titre (GMT), seroconversion rate (SCR; defined as percentage of subjects achieving an increase in HI titers from <1:10 to ≥1:40 or at least a 4-fold post-vaccination increase in HI titer from a pre-vaccination titer ≥1:10), seroprotection rate (SPR; percentage of subjects with HI titers ≥1:40 following vaccination), and Mean Geometric Increase (MGI; geometric mean of the ratio between post-vaccination and pre-vaccination reciprocal HI titers). Subjects with HI antibody titers of ≥1:10 were considered to be seropositive.

2.4. Reactogenicity and safety assessments

The secondary reactogenicity and safety endpoints were assessed in both study groups.

Solicited local and general symptoms were assessed during the 7-day post-vaccination period after each dose. Subjects recorded the occurrence and severity of solicited events on diary cards. Local (injection site) symptoms were pain, redness, and swelling,