

A Phase II, randomized, controlled, observer-blind, single-center study to evaluate the immunogenicity, safety and tolerability of two doses of MF59[®]-adjuvanted H5N1 influenza vaccine, AFLUNOV[®], in subjects aged 6 months to 17 years

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Background and Aim: It is not yet known which age group will be most affected by the next pandemic virus. Therefore, influenza pre-pandemic and pandemic vaccines must demonstrate safety and immunogenicity in all age groups. This has already been shown by AFLUNOV in adults and the elderly. The present study established the immunogenicity, safety, and tolerability of two doses of MF59-adjuvanted H5N1 vaccine (MF59–H5N1) administered 3 weeks apart in subjects aged 6 months to 17 years compared with a seasonal trivalent influenza vaccine (FLUAD[®]).

Methods: This prospective, randomized, controlled, observer-blind Phase II study was performed in Finland. A total of 472 subjects aged 6 months to 17 years were enrolled and divided into three cohorts: toddlers aged 6 to < 36 months, children aged 3 to < 9 years, and adolescents aged 9 to < 18 years. Each age group was randomized in a 3:1 ratio to receive either two 0.5 mL doses of MF59–H5N1 influenza vaccine or two 0.25 mL (subjects < 3 years of age) or 0.5 mL (subjects ≥ 3 years of age) doses of FLUAD. Hemagglutination inhibition (HI), single radial hemolysis (SRH), and microneutralization (MN) antibody responses were measured using standard methods.

Results: Immunogenicity: Of the 472 subjects enrolled, 471 were vaccinated. Of these 334 subjects received MF59–H5N1 and 137 subjects received Flud. Baseline and other demographic characteristics were similar between the two treatment groups for the all-randomized, per-protocol and subset populations. HI results after the primary course of vaccination demonstrated that two CHMP (The Committee for Medicinal Products for Human Use)¹ criteria were reached by the adolescent group and one was reached by the toddler and children groups. In addition, SRH results showed that after the first dose all three cohorts fulfilled CHMP criteria for GMR (geometric mean ratio) and seroconversion. After the second vaccination (day 43), all three CHMP immunogenicity criteria were met for MF59–H5N1 in all three age groups. Similarly, all CHMP criteria were met in all age groups for MF59–H5N1 vaccination by SRH. There is no recognized correlate of protection for MN; however, a fourfold increase in MN titer after vaccination has been used by others to denote seroprotection to H5 viral antigens.^{2,3} After the second vaccination, 94% of toddlers, 92% of children, and 72% of adolescents in the MF59–H5N1 group achieved at least a fourfold increase in MN titer over baseline and 99% of toddlers, children, and adolescents achieved an MN titer ≥ 40.

Safety and tolerability: Of the 472 vaccinated subjects, 471 were included in the safety analysis: 334 subjects immunized with MF59–H5N1 (145 toddlers, 96 children, 93 adolescents) and 137 subjects immunized with FLUAD (56 toddlers, 40 children, 41 adolescents). Across the two vaccinations, the proportion of children and adolescent subjects with reported local reactions were similar between MF59–H5N1 and FLUAD groups.

Toddlers 6 to <36 months of age: Overall reactogenicity was highest after the first vaccination and decreased after the second vaccination. A total of 76% of MF59–H5N1 and 75% of Flud recipients after first injection and 68% of MF59–H5N1 and 63% of Flud recipients after second vaccination reported at least one solicited local or systemic reaction. Most solicited reactions were mild or moderate, with no more than 2% of each solicited local or systemic reaction classified as severe in either vaccine group. Erythema (21% to 33%) after any injection and tenderness (21% to 29% after any injection) were the most common solicited local reactions and irritability (20% to 39% after any injection) was the most common solicited systemic reaction in both vaccine groups. No death or AE leading to a subject's withdrawal from the study was reported. Within this age cohort, there was one subject who reported one SAE (hospitalization due to acute pyelonephritis) but it was assessed as not related to the study vaccines.

Children 3 to <9 years of age: A total of 72% MF59–H5N1 and 80% of Flud recipients, after first injection and 68% of MF59–H5N1 and 56% of Flud recipients after second injection, reported at least one solicited local or systemic reaction. Most solicited reactions were mild or moderate, with no more than 5% of each solicited local or systemic reaction classified as severe in either vaccine group, most of them were transient. Pain (36% to 53% after any injection) was the most common solicited local reaction, no more than 5% children complained of severe pain after any injection, and headache (9% to 23% after any injection) was the most common systemic reaction in both vaccine groups. The proportion of subjects reporting any solicited local or systemic reactions were similar between the two vaccine groups. No death or AE leading to a

subject's withdrawal from the study was reported during the study. One subject reported one SAE, (hospitalization due to moderate renal injury) was assessed as not related to the study vaccines.

Adolescents 9 to <18 years of age: A total of 91% of MF59- H5N1 and 88% of Fluvad recipients after first injection and 82% of Fluvad-H5N1 and 78% of Fluvad recipients, after second injection, reported at least one solicited local or systemic reaction. Most solicited reactions were mild or moderate, with no more than 5% of each solicited local or systemic reaction classified as severe in either vaccine group, most of them were transient.

Pain (63% to 78% after any injection) was the most common local reaction, no more than 5% of adolescents complained of severe pain, and headache (22% to 59% after any injection) the most common solicited systemic reaction in both vaccine groups. The proportion of subjects reporting any solicited local or systemic reactions were similar between the two vaccine groups.

No death or AE leading to a subject's withdrawal from the study was reported during the study. There were no reported SAEs.

Conclusion: AFLUNOV, an MF59-adjuvanted H5N1 vaccine in development, was immunogenic in all age groups tested regardless of baseline titers and assay used for serologic assessment. All CHMP immunogenicity criteria³ were reached for the age groups tested at day 43. Local and systemic reactogenicity was mainly of mild to moderate severity. The study confirms that the MF59–H5N1 vaccine is immunogenic and safe for use in pre-pandemic vaccine programs in children.

References: 1 European Committee for Medicinal Products. EMEA/CHMP/VWP/26399/2006; 2. Treanor J, *et al. N Engl J Med* 2006; **354**:1343–1351; 3 Bresson J, *et al. Lancet* 2006; **367**:1657–1664.