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Original Article

Safety of the Northern Hemisphere 2014/2015 formulation of the inactivated split-virion intramuscular trivalent influenza vaccine

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ABSTRACT

In the current study, the safety of the 2014/2015 Northern Hemisphere formulation of Vaxigrip® (Sanofi Pasteur) was assessed to satisfy European Union requirements. Individuals ⩾6 months of age eligible for seasonal influenza vaccination were included. Children 6 months–8 years of age received one dose (0.25 ml for 6–35 mo; 0.5 ml for 3–8 y) on day 0, and those who were previously unvaccinated received a second dose of the same volume on day 28. Participants ⩾9 years of age received one full dose (0.5 ml) on day 0. Frequency categories for solicited reactions were compared with historical data for the closest age group available. A total of 527 participants were included (6 mo–5 y, n = 106; 6–12 y, n = 105; 13–17 y, n = 106; 18–65 y, n = 105; >65 y, n = 105). Frequency categories were higher in this study than for the historical comparator for fever (very common vs. common) in participants 6 months–5 years of age; shivering (very common vs. common), rash (uncommon vs. very rare), and grade 3 injection-site induration (common vs. uncommon) in participants 6–12 years of age; and shivering in participants 13–17 years of age (very common vs. common) and >65 years of age (very common vs. common). However, these increases were not considered clinically significant because confidence intervals for proportions were overlapping and because most of the reactions were of grade 1 to 2 and resolved rapidly and spontaneously. No treatment-related serious adverse events were recorded and no safety concerns or safety signals were detected. These results indicate that the 2014/2015 Northern Hemisphere formulation of Vaxigrip was well tolerated and safe to use in all age groups, with no specific concerns identified, although the study was not powered to detect rare or very rare events.

Abbreviations: 95% CI, 95% confidence interval; AE, adverse event; EMA, European Medicines Agency; SAE, serious adverse event.

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1. Introduction

Influenza virus undergoes frequent changes to its surface antigens, a process known as antigenic drift [1]. As a consequence, influenza vaccine formulations must be adjusted each year. Each February, the World Health Organization recommends the qualitative composition of Northern Hemisphere influenza vaccines for the next influenza season based on the location of outbreaks and the strains responsible for them [2], and in March, the Commission of the European Union provides the final recommendations for the vaccine composition to manufacturers [3].

Since 1968, Sanofi Pasteur has been producing an inactivated split-virion trivalent influenza vaccine (Vaxigrip®) [4]. In compliance with World Health Organization and European Medicines Agency (EMA) recommendations for seasonal influenza vaccine design, Vaxigrip contains two variants of influenza subtype A (H1N1 and H3N2) and one variant of type B. Vaxigrip reduces the incidence of influenza infection, decreases workplace absenteeism, and decreases hospitalization and mortality in the elderly and other at-risk populations [5]. Long-term experience has also shown that this trivalent influenza vaccine is well tolerated [6] and does not increase the rate of clinically important medically attended events compared with no vaccination [7,8].

In April 2014, the Pharmacovigilance Risk Assessment Committee of the EMA adopted a new guidance (EMA/PRAC/222346/2014) for the enhanced safety surveillance of seasonal influenza vaccines in the European Union [9]. This guidance outlined safety requirements that were to be set up as a pilot for the Northern Hemisphere 2014/2015 influenza season. We describe here the results of an open-label, uncontrolled, multicenter, phase IV study conducted to satisfy these requirements for the 2014/2015 Northern Hemisphere formulation of Vaxigrip. The trial was conducted as recommended in the guidance and in all age groups for which influenza vaccination is indicated.

2. Material and methods

2.1. Study design

This was an open-label, uncontrolled, phase IV study (EudraCT No. 2014-000628-68) conducted at 16 centers in France. In accordance with EMA guidance EMA/PRAC/222346/2014, the primary objectives were (a) to detect potential increases in reactogenicity and allergic events compared to historical data on Vaxigrip and (b) to rapidly detect clinically significant changes in the frequency and/or severity of expected reactogenicity within 7 days after injection of one dose of the Northern Hemisphere 2014/2015 formulation of Vaxigrip in all age groups in which it is indicated. The secondary objective was to describe serious adverse events (SAEs) occurring throughout the study. The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice as well as local and national laws. All participants or legal representatives provided signed informed consent before taking part in the trial. For children, whenever possible, informed consent was also obtained from the child.

2.2. Participants

Individuals ⩾6 months of age were considered for inclusion. Participants had to be eligible for influenza vaccination and could not have any of the contraindications listed in the Summary of Product Characteristics for the intramuscular influenza vaccine. They could not be hypersensitive to any of the vaccine components or have febrile illness or an acute infection at enrolment. Participants were recruited in five age groups (6 mo–5 y, 6–12 y, 13–17 y, 18–65 y, and >65 y) of 105 participants each.

2.3. Study conduct

Participants were injected via the intramuscular or deep subcutaneous route with the 2014/2015 Northern Hemisphere formulation of the inactivated split-virion intramuscular trivalent influenza vaccine (Vaxigrip, Sanofi Pasteur, Lyon, France). Each 0.5 ml contained 15 μg hemagglutinin per strain from A/California/7/2009 (H1N1)pdm09-like, A/Texas/50/2012 (H3N2)-like, and B/Massachusetts/2/2012-like viruses. The vaccine does not contain adjuvants or preservatives. Children 6 months–8 years of age received one dose (0.25 ml for 6–35 mo; 0.5 ml for 3–8 y) on day 0, and those who were previously unvaccinated received a second dose of the same volume on day 28. Participants ⩾9 years of age received one full dose (0.5 ml) on day 0. After each vaccination, participants were kept under observation for 20 min to ensure their safety in the case of allergic or other immediate reactions.

Participants or their parents or legal representatives recorded information about solicited reactions, unsolicited adverse events (AEs), and SAEs for up to 7 days after each vaccination on a diary card. Injection-site reactions included pain/tenderness, erythema, swelling, induration, and ecchymosis. Systemic reactions included fever, vomiting, abnormal crying, drowsiness, decreased appetite, irritability, and rash for children 6–23 months of age; abnormal crying, irritability, fever, headache, malaise, myalgia, shivering, rash, vomiting, nausea, arthralgia, decreased appetite for children 2–5 years of age; and fever, headache, malaise, myalgia, shivering, rash, vomiting, nausea, arthralgia, and decreased appetite for participants ⩾6 years of age. Solicited reactions were graded from 1 for least severe to 3 for most severe as detailed in Supplemental Tables 1 and 2.

Safety was evaluated in accordance with the EMA/PRAC/222346/2014 Interim Guidance on Enhanced Safety Surveillance [9]. Unsolicited AEs were encoded using MedDRA version 17 and were considered grade 1 for no interference with activity, grade 2 for some interference with activity, and grade 3 for significant, prevents daily activity. The investigator assessed the causal relationship between each unsolicited systemic AE and vaccination as either not related or as related/possibly related.

Solicited reaction frequency categories were assigned as follows: very common for ⩾10%, common for ⩾1% to <10%, uncommon for ⩾0.1% to <1%, rare, for ⩾0.01% to <0.1%, and very rare for <0.01%. Historical frequencies were based on completed Vaxigrip clinical trials for participants ⩾3 years of age (ClinicalTrials.gov No. NCT01481454) [10] and EudraCT Nos. 2011-005374-33, 2011-001976-21 [11], 2012-005242-37, 2009-017690-38, and 2011-005325-42). For children ⩽2 years of age, historical frequencies were based on a retrospective survey of febrile events [12]. Further detail on the selection of historical comparators is provided in the Supplemental methods.

2.4. Sample size

The sample size was determined in accordance with the EMA/PRAC/222346/2014 Interim Guidance on Enhanced Safety Surveillance. The recommendation is to have at least 100 evaluable participants per age group. Thus, no sample size calculation was made. Based on previous experience in influenza vaccine trials and considering the planned duration of each participant's participation, a maximum 5% drop out rate was anticipated. To ensure a total of 100 evaluable participants per age, 105 participants were therefore planned for each age group. Accordingly, the study was not powered to detect rare (⩾0.01% to <0.1%) or very rare (<0.01%) events.