Vaccine 35 (2017) 2745–2752

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Immunogenicity and safety of a quadrivalent inactivated influenza virus vaccine compared with a comparator quadrivalent inactivated influenza vaccine in a pediatric population: A phase 3, randomized noninferiority study

Jolanta Airey [a,*], Frank R. Albano [a], Daphne C. Sawlwin [b], Alison Graves Jones [b], Neil Formica [a], Vince Matassa [a], Jane Leong [c]

[a] Clinical Development, Seqirus Pty Ltd, Parkville, Victoria, Australia
[b] Global Pharmacovigilance and Risk Management, Seqirus Pty Ltd, Parkville, Victoria, Australia
[c] Medical Affairs, Seqirus Pty Ltd, Parkville, Victoria, Australia

ARTICLE INFO

Article history:
Received 6 December 2016
Received in revised form 24 February 2017
Accepted 6 March 2017
Available online 5 April 2017

Keywords:
Immunogenicity
Inactivated
Influenza vaccine
Children
Quadrivalent
Safety

ABSTRACT

Background: Seqirus 2010 Southern Hemisphere split-virion trivalent inactivated influenza vaccine (IIV3) was associated with increased febrile reactions in children. Studies in vitro concluded that increasing concentrations of splitting agent decreased residual lipids and attenuated proinflammatory cytokine signals associated with fever. We assessed immunogenicity and safety of a quadrivalent inactivated influenza vaccine (IIV4; produced using higher concentration of splitting agent) versus a United States-licensed comparator IIV4 in healthy children aged 5–17 years.

Methods: Participants (N = 2278) were randomized 3:1 and stratified by age (5–8 years; 9–17 years) to receive IIV4 (n = 1709) or comparator IIV4 (n = 569). Primary objective was to demonstrate noninferiority of IIV4 versus comparator IIV4 as assessed by hemagglutination inhibition (HI) geometric mean titer (GMT) ratio (upper bound of two-sided 95% confidence interval [CI] $\leq$ 1.5) and difference in seroconversion rate (upper bound of two-sided 95% CI $\leq$ 10%) for all four vaccine strains. HI antibody titers were assessed at baseline and 28 days postvaccination. Solicited and unsolicited adverse events were assessed during each 7- and 28-day postvaccination period, respectively.

Results: IIV4 met immunogenicity criteria for noninferiority. Adjusted GMT ratios (comparator IIV4/IIV4) for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains were 1.01 (95% CI; 0.93, 1.09), 1.05 (0.96, 1.15), 0.89 (0.81, 0.98), and 0.92 (0.83, 1.02), respectively. Corresponding values for differences (95% CI) in seroconversion rates (comparator IIV4 minus IIV4) were −3.1 (−8.0, 1.8), 0.4 (−4.5, 5.3), −3.4 (−8.3, 1.5), and −2.0 (−6.9, 2.9). Fever rates were numerically higher, but not statistically different, with IIV4 versus comparator IIV4. No new safety signals were reported.

Conclusion: IIV4 demonstrated immunological noninferiority to the comparator IIV4 with a clinically acceptable safety profile in children aged 5–17 years. Increased levels of virus splitting agent seem to have reduced fever rates observed in children with Seqirus IIV3, particularly those aged 5–8 years.

Funding: Seqirus Pty Ltd; Clinicaltrials.gov identifier: NCT02545543.

1. Introduction

Type B influenza causes 20–25% of influenza infections worldwide [1] and is associated with substantial morbidity and mortality in children [2]. There is a need for influenza vaccines that protect against different B strain lineages. Switching from the conventional trivalent inactivated influenza vaccine (IIV3) to a quadrivalent inactivated influenza vaccine (IIV4) that includes both influenza B lineages (Victoria and Yamagata) increases the likelihood of adequate protection against influenza B [1].

Abbreviations: AE, adverse event; CI, confidence interval; FAS, full analysis set; GMFI, geometric mean fold increase; GMT, geometric mean titer; HI, hemagglutination inhibition; IIV3, trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccine; SAE, serious adverse event; SCR, seroconversion rate; SD, standard deviation; SPR, seroprotection rate; TDOC, taurodeoxycholate; US, United States.

* Corresponding author at: Clinical Development, Seqirus Pty Ltd, 63 Poplar Road, Parkville, Victoria 3052, Australia.
E-mail address: jolanta.airey@seqirus.com (J. Airey).

http://dx.doi.org/10.1016/j.vaccine.2017.03.028
0264-410X/

In the 2010 Southern Hemisphere influenza vaccination season, Seqirus/CSL IIV3 (A/California/07/2009 [H1N1], A/Wisconsin/15/2009 [H3N2], and B/Brisbane/60/2008 [B strain]) was associated with unexpected reports of fever and febrile seizures in children in Australia and New Zealand, predominantly in those under 5 years of age, leading to suspension of its use in children in this age group [3]. Increased incidences of febrile reactions in children aged 5–9 years were also reported [3]. Seqirus conducted extensive scientific investigations in vitro and concluded that degraded RNA fragments delivered by residual lipids activated the release of proinflammatory cytokines, which stimulated the pyrogenic response in children. Further, it was established that by increasing the level of sodium taurodeoxycholate (TDOC) to split the B strain in particular resulted in decreased levels of residual lipids and attenuated proinflammatory cytokine signals [4].

A subsequent phase 4, randomized study showed that overall (≥100.4°F/≥38.0 °C) and severe (≥102.2°F/≥39.0 °C) fever rates (8.2% and 2.1%, respectively) for the 2014–2015 Northern Hemisphere modified Seqirus IIV3 with the B strain split at 1.5% w/v TDOC concentration (within current manufacturing parameters) were similar to those for a United States (US) licensed reference IIV4 (Fluzone Quadrivalent; 9.2% and 4.1%, respectively) in healthy children aged 5–8 years [5]. Further, these fever rates with the modified IIV3 were lower than those previously reported (overall: 16%; severe: 5%) in pediatric clinical studies of the IIV3 used before 2010 [6].

Seqirus IIV4 (hereafter referred to as IIV4) is an egg-derived, inactivated, split-virion influenza virus vaccine with all four strains (Type A [H1N1]-like virus, Type A [H3N2]-like virus, Type B [Victoria lineage], Type B [Yamagata lineage]) split at 1.5% w/v TDOC (within current manufacturing parameters) to reduce residual lipid content and the associated potential for pyrogenic vaccine responses. The primary objective of this phase 3, randomized, observer-blinded study was to determine if IIV4 elicits an immune response that is noninferior to a US-licensed 2015–2016 comparator IIV4 containing the same virus strains as IIV4 in healthy children 5–17 years of age. The study also characterized the immunogenicity and safety (particularly fever events) of both vaccines stratified by age (5–8 years; 9–17 years).

2. Materials and methods

2.1. Study design

This phase 3, randomized, observer-blinded, comparator-controlled, multicenter study evaluated IIV4 against an US-licensed 2015–2016 comparator IIV4 containing the same influenza strains recommended by the US Food and Drug Administration (FDA) and the Vaccines and Related Biological Products Advisory Committee [7] for inclusion in the Northern Hemisphere 2015–2016 season. The study was conducted in 32 centers in the US between September 2015 and June 2016, and was approved by a central Institutional Review Board. The study was conducted in accordance with standards of Good Clinical Practice [8], as defined by the International Conference on Harmonisation, the principles of the Declaration of Helsinki [9], and all applicable federal and local regulations. Written informed consent from parents/guardians and participant assent (where appropriate) was obtained before any study-related procedures. The study was sponsored by Seqirus and is registered at ClinicalTrials.gov: NCT02545543.

2.2. Study population

Study participants included healthy male and female children 5–17 years of age. Participants were excluded if they were febrile (oral temperature ≥100.0°F/≥37.8 °C), acutely ill, immunocompromised, allergic to egg proteins or any study vaccine component, had a history of serious adverse reactions to any influenza vaccine, had a known coagulation disorder, had received any influenza vaccine within the last 6 months, had received any immunoglobulin or blood product within the last 3 months, or had received an investigational product within the last 28 days.

2.3. Randomization

Eligible participants were randomized 3:1 to receive either IIV4 or comparator IIV4. Randomization was conducted using an interactive response technology system and was stratified by age to one of two cohorts: (i) 5 to 8 years of age (5–8 year cohort) and (ii) 9–17 years of age (9–17 year cohort).

2.4. Vaccines and vaccination schedule

Both IIV4 (Afluria Quadrivalent™/Afluria Quad™: lot number: 090403401) and the comparator IIV4 (Fluarix Quadrivalent, GlaxoSmithKline Biologicals: lot number: 4A5K3) contained a total of 60 mcg of hemagglutinin (HA) in the recommended amount of 15 mcg HA for each influenza virus strain: Type A (H1N1)-like virus, Type A (H3N2)-like virus, Type B (Victoria lineage), and Type B (Yamagata lineage). Administration was via intramuscular (deltoid) injection (0.5 mL per dose). Participants were observed for 30 min postvaccination. Participants were scheduled to receive either a single vaccination regimen (Day 1) or a two-vaccination regimen (Day 1 and Day 29 + 4; 5–8 year cohort only), according to the 2015–2016 recommendations of the US Advisory Committee on Immunization Practices guidelines for seasonal influenza vaccination [10].

2.5. Immunogenicity endpoints

2.5.1. Primary immunogenicity endpoints

The immunogenicity of both study vaccines was assessed at baseline and 28 days after the last vaccine administration by measuring the hemagglutination inhibition (HI) antibody titers to the four viral strains included in the vaccines. Serology specimens were collected at Visit 1 (Day 1) before first study vaccination and at least 28 days after last study vaccination at Study Exit Visit (Visit 2 [Day 29 + 4] for participants receiving a single dose or Visit 3 [Day 29 + 4 after Visit 2] for participants receiving two doses). The noninferiority immunogenicity of IIV4 relative to comparator IIV4 was assessed by eight co-primary endpoints of HI geometric mean titer (GMT) and seroconversion rate (SCR) for each viral strain as follows: (1) GMT ratio defined as the geometric mean of the postvaccination (28 days after last vaccination) HI titer for the comparator IIV4 over the geometric mean of the postvaccination HI titer for IIV4; and (2) difference in SCR between the comparator IIV4 and IIV4 where SCR was defined as the percentage of participants with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40, or a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer.

2.5.2. Secondary immunogenicity endpoints

Immune responses were characterized by seroprotection rates (SPRs), SCRs, and geometric mean fold increase (GMFI) in antibody titer by study vaccine and by age cohort. SPR was defined as the percentage of participants with an HI titer ≥40. GMFI in antibody titer was defined as the geometric mean of the fold increase of postvaccination HI antibody titer over the prevaccination HI antibody titer.