Trials in Vaccinology 5 (2016) 48–52

Contents lists available at ScienceDirect

Trials in Vaccinology

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

Original Article

Immunogenicity and safety of a quadrivalent influenza vaccine in children and adolescents in Taiwan: A phase III open-label trial ☆

Chun-Yi Lu [a], Chantal Ferracin [b,1], Cheng-Hsun Chiu [c,*], Nathalie Lavis [b,*], Chiung-Hua Huang [d], Li-Min Huang [a]

[a] Department of Pediatrics, National Taiwan University Hospital, No. 7, Chung Shan S. Rd., Zhongzheng Dist., Taipei City 10002, Taiwan, ROC
[b] Sanofi Pasteur, 2 Pont Pasteur, 69367 Lyon Cedex 07, France
[c] Chang Gung Memorial Hospital, Chang Gung University, No. 5, Fu-Shin Street, Kweishan 333, Taoyuan, Taiwan, ROC
[d] Sanofi Taiwan, 12th Fl., No. 337 Fu Hsing N. Rd., Taipei 10544, Taiwan, ROC

ARTICLE INFO

Article history:
Received 29 June 2015
Revised 14 January 2016
Accepted 12 February 2016
Available online 2 March 2016

Keywords:
Quadrivalent influenza vaccine
Children
Adolescents

ABSTRACT

Until recently, all seasonal influenza vaccines have been trivalent, containing strains A(H1N1), A(H3N2), and one of the two B strain lineages (Yamagata or Victoria), resulting in frequent mismatches between the circulating B strain lineage and that included in the vaccine. A quadrivalent, inactivated, split-virion influenza vaccine (IIV4) containing strains from both B lineages has been developed to address this. We performed an open-label phase III study to assess the immunogenicity and safety of the 2013–2014 Northern Hemisphere formulation of IIV4 in children and adolescents 9–17 years of age in Taiwan. Participants were vaccinated with one dose of IIV4 by intramuscular or deep subcutaneous injection. Hemagglutinin inhibition (HAI) titers were measured before and 21 days after vaccination. Solicited injection-site and systemic reactions were assessed for up to 7 days after vaccination, and adverse events (AEs) were recorded until day 21. One hundred participants were included. Despite relatively high pre-vaccination titers, post-vaccination HAI titers increased for all four strains, with geometric mean ratios (day 21/day 0) of 2.29 for A(H1N1), 2.05 for A(H3N2), 3.33 for B/Massachusetts (Yamagata lineage), and 4.59 for B/Brisbane (Victoria lineage). Post-vaccination seroprotection rates were 99% for A(H3N2) and 100% for A(H1N1), B/Massachusetts, and B/Brisbane. Due to high pre-vaccination titers, rates of seroconversion/significant increase of HAI titer were relatively low at 24% for A(H1N1), 20% for A(H3N2), 39% for B/Massachusetts, and 48% for B/Brisbane. Injection-site pain (56%), myalgia (45%), and malaise (15%) were the most frequently reported solicited reactions, and most solicited reactions were mild or moderate. No treatment-related AEs, immediate unsolicited AEs, unsolicited non-serious injection-site AEs, grade 3 unsolicited AEs, or serious AEs were reported. In conclusion, this study showed that the 2013–2014 Northern Hemisphere formulation of the intramuscular IIV4 was immunogenic and well tolerated by children and adolescents 9–17 years of age.

1. Introduction

Since the 1980s, two distinct genetic lineages of influenza B virus, Victoria and Yamagata, have been co-circulating worldwide [1,2]. Both B lineages cause similar influenza illnesses. Until recently, all vaccines for seasonal influenza were trivalent and contained two A strains (H1N1, and H3N2) and one B strain lineage. This has resulted in frequent mismatches between the circulating B virus and that included in the vaccine, reducing vaccine effectiveness. For example, in half of the Northern hemisphere influenza seasons between 1999/2000 and 2012/2012, the B strain included in the trivalent vaccine was not the same lineage as the dominant circulating B strain [3].

Quadrivalent influenza vaccines containing both B lineages have been developed and should help address the problem of B

☆ *Clinical trial registry*: WHO Universal Trial No. U1111-1127-7693.

* Corresponding authors at: Department of Pediatrics, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, No. 5, Fu-Shin Street, Kweishan 333, Taoyuan, Taiwan, ROC (C.-H. Chiu). Sanofi Pasteur, 2 Avenue Pont Pasteur, 69367 Lyon Cedex 07, France (N. Lavis).

E-mail addresses: cylu@ntu.edu.tw (C.-Y. Lu), alba1582@gmail.com (C. Ferracin), chchiu@adm.cgmh.org.tw (C.-H. Chiu), nathalie.lavis@sanofipasteur.com (N. Lavis), Dephanie.Huang@sanofi.com (C.-H. Huang), lmhuang@ntu.edu.tw (L.-M. Huang).

[1] Current address: MSA, 35 rue du Plat, 69002 Lyon, France.

http://dx.doi.org/10.1016/j.trivac.2016.02.002
1879-4378/

strain selection [4,5]. Sanofi Pasteur has developed a quadrivalent, inactivated, split-virion influenza vaccine (IIV4)[2] containing 15 μg of hemagglutinin from the A(H1N1) and A(H3N2) strains, and B strains from both lineages. Phase III clinical trials comparing IIV4 and the inactivated trivalent influenza vaccine (IIV3; Vaxigrip®, Sanofi Pasteur) have been completed in French and German adults [6], in children 3–8 years of age in Poland, Finland, Mexico, and Taiwan (EudraCT No. 2011-005101-79; unpublished observations), and in children/adolescents 9–17 years of age and adults 18–60 years of age in the Asia-Pacific area [7]. These studies showed that the immunogenicity of IIV4 was non-inferior to IIV3 for the three common strains and superior for the additional B strain. The studies also showed similar safety profiles for IIV4 and the trivalent comparator.

To comply with registration requirements in Taiwan, we performed a phase III study assessing the immunogenicity and safety of the 2013–2014 Northern Hemisphere formulation of IIV4 in children and adolescents 9–17 years of age.

2. Material and methods

2.1. Study design

This was a phase III open-label, uncontrolled trial conducted at National Taiwan University Hospital (Taipei, Taiwan R.O.C.) and Chang Gung Children's Hospital (Taoyuan, Taiwan R.O.C.) (WHO Universal Trial No. U1111-1127-7693). The objectives were to describe the immunogenicity and safety of the IIV4 2013–2014 Northern Hemisphere seasonal formulation in children and adolescents. The study was approved by the institutions' ethics committees and was conducted in compliance with International Conference on Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from parents or legal guardians before inclusion of participants in the study.

2.2. Study participants

Participants had to be 9–17 years of age. Girls could not be pregnant or lactating and could not be of childbearing potential or had to be using an effective method of birth control if sexually active. Participants were excluded for the following reasons: receipt of any vaccine in the 4 weeks preceding the trial vaccination or planned receipt of any vaccine in the 3 weeks following receipt of the trial vaccine; vaccination against influenza in the previous 12 months if administered in the context of a clinical trial or in the previous 6 months if administered in the context of an influenza vaccination campaign; receipt of immune globulins, blood, or blood-derived products in the past 3 months; known or suspected congenital or acquired immunodeficiency; receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months); self-reported history of seropositivity for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus; hypersensitivity to any of the vaccine components or history of a life-threatening reaction to the vaccine used in the study or to a vaccine containing any of the same substances; known or suspected thrombocytopenia; bleeding disorder or receipt of anticoagulants in the 3 weeks preceding inclusion; alcohol abuse or drug addiction; chronic illness that was at a stage where it might interfere with trial conduct or completion; or moderate or severe acute illness or infection on the day of vaccination or febrile illness (temperature $\geqslant$38.0 °C)

2.3. Vaccine

IIV4 was a quadrivalent split virion, inactivated influenza vaccine and was produced by Sanofi Pasteur (Lyon, France). Each 0.5-ml dose was provided in a prefilled syringe and contained 15 μg of each hemagglutinin for the A/California/7/2009 (H1N1) pdm09, A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage) strains.

2.4. Study conduct

All participants were vaccinated with one dose (0.5 ml) of IIV4 by the intramuscular or deep subcutaneous route. All subjects provided a pre-vaccination baseline blood sample (5 ml) and a second blood sample (5 ml) at day 21 ± 3.

2.5. Immunogenicity endpoints

Immunogenicity endpoints were as defined by the Committee for Medicinal Products for Human Use Note for Guidance CPMP/BWP/214/96 and, as described previously [6,7], included geometric mean titers (GMTs), geometric mean of individual titer ratio of post-vaccination (day 21) vs. pre-vaccination (day 0) (GMTRs), detectable hemagglutination inhibition (HAI) titer ($\geqslant$10), seroprotection (HAI titer $\geqslant$40), and seroconversion or significant increase in HAI titer. Seroconversion was defined as a HAI titer <10 on day 0 and a HAI titer $\geqslant$40 on day 21, and significant increase was defined as a HAI titer $\geqslant$10 on day 0 and a $\geqslant$4-fold increase in HAI titer on day 21. HAI titers were measured as described previously [6] at Focus Diagnostics, Inc. (Cypress, CA). Briefly, the highest serum dilution resulting in complete inhibition of hemagglutination was determined in two independent assay runs for each sample. The titer for each sample was calculated as the geometric mean of the reciprocal of the duplicate values. The lower limit of quantitation was set at the reciprocal of the lowest dilution used in the assay (10), and the upper limit of quantitation as the highest dilution used in the assay (10,240).

2.6. Safety endpoints

Subject, parents, or guardians recorded the daily temperature and the presence and intensity grade of solicited injection-site reactions (pain, erythema, swelling, induration, and ecchymosis) and systemic reactions (fever, headache, malaise, myalgia, and shivering) up to day 7 on diary cards. For children 9–11 years of age, erythema, swelling, induration, and ecchymosis were considered grade 1 for >0 to <25 mm, grade 2 for 25 to <50 mm, and grade 3 for $\geqslant$50 mm; and in children and adolescents 12–17 years, they were considered grade 1 for 25 to $\leqslant$50 mm, grade 2 for 51 to $\leqslant$100 mm, and grade 3 for >100 mm. Fever was considered grade 1 for 38.0–38.4 °C, grade 2 for 38.5–38.9 °C, and grade 3 for $\geqslant$39 °C. Injection-site pain, headache, malaise, myalgia, and shivering were considered grade 1 for easily tolerated or no interference with daily activity, grade 2 for sufficiently discomforting to interfere with normal behavior or daily activities, and grade 3 for significant, prevents normal daily activities.

Participants were followed-up by investigators for unsolicited adverse events (AEs) until day 21 ± 3 according to International Conference on Harmonisation E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. AEs were coded using MedDRA version 14 (MedDRA MSSO, McLean, VA, USA). Unsolicited AEs were considered grade 1 for no interference with activity, grade 2 for some interference

[2] AE, adverse event; CI, confidence interval; GMT, geometric mean titer; GMTR, geometric mean ratio of the day 21 vs. day 0 titer; HAI, hemagglutination inhibition; IIV3, inactivated trivalent influenza vaccine; IIV4, inactivated tetravalent influenza vaccine; SAE, serious adverse event.