



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Influenza virus haemagglutinin

Proprietary Product Name: Fluarix Tetra

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of first round report: 16 May 2017

Date of second round report: 17 December 2017

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
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List of common abbreviations

Abbreviation	Meaning
AE	Adverse event
AESIs	Adverse events of special interest
AIVC	Australian Influenza Vaccine Committee
AOM	Acute otitis media
ASA	Australian-specific annex
ATP-E	According-to-protocol efficacy
CBER	Centre for Biologics Evaluation and Research
CDC	Centres of Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
D-QIV	Fluarix Tetra
ELISA	Enzyme linked immunosorbent assay
ESS	Enhanced safety surveillance
EU	European Union
FDA	Food and Drug Administration
Fluarix Tetra IP	Fluarix Tetra from investigational process (IP)
Fluarix Tetra LP	Fluarix Tetra from licensed process (LP)
GBS	Guillain Barré syndrome
GCP	Good Clinical Practice
GMTs	Geometric Mean Titres
Gp	Group
HA	Haemagglutinin
HI	Haemagglutination Inhibition
ICH	International Conference on Harmonization

Abbreviation	Meaning
ILI	Influenza like Infection
IM	Intramuscular
ITT	Intention to treat
LAR	Legally authorised representative.
LRI	Low respiratory infection
MEDRA	Medical Dictionary for Regulatory Activities
MAVs	Medically attended visits
MGI	Mean geometric increase
PBRER	Period Benefit Risk Evaluation Report
PI	Prescribing Information
pIMDs	potential Immune-Mediated-Diseases
PP	Per protocol
PT	Preferred Term
QIV	Quadrivalent inactivated Influenza Vaccine
RMP	Risk Management Plan
RRA	Recruitment/Randomisation agreement
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SD	Standard deviation
SH	Southern Hemisphere
SOC	System Organ Class
SPR	Seroprotection Rate
TGA	Therapeutic Goods Administration
TRAE	Treatment-related adverse event

Abbreviation	Meaning
TVC	The total vaccinated cohort
URTI	Upper respiratory tract infection
US	United States
VE	Vaccine Efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organisation

1. Submission details

1.1. Identifying information

Submission number	PM-2017-01036-1-2
Sponsor	GlaxoSmithKline (GSK) Australia Pty Ltd
Trade name	Fluarix Tetra
Active substance	Influenza virus haemagglutinin (x 4)

1.2. Submission type

This is an application to extend the indication for GlaxoSmithKline Australia Pty Ltd's inactivated Quadrivalent Influenza Vaccine (Fluarix Tetra) (D-QIV) for active immunisation of adults and children from 3 years of age, to adults and children from 6 months of age.

The sponsor has submitted the data in support of this application from the Pivotal Study D-QIV-004, a Phase III, observer blind, randomised efficacy study with non-influenza vaccine controls that enrolled a total of 12,046 subjects (6 to 35 months of age) in five independent cohorts.

In addition, data from two supporting studies are included in this application.

- The Phase III Study D-QIV-009, an extension to D-QIV-004 designed to evaluate the adequacy of the immunological priming of children 6 to 35 months of age.
- The Phase III, double-blind, randomised, multicentre Study D-QIV-015 assessed the safety and immunogenicity of Fluarix Tetra manufactured with a new process, in which the downstream processes were harmonised for all monovalent bulks. This study was under evaluation by the TGA at the time of this evaluation. While D-QIV-015 included 3 age cohorts, only results for the 6 to 35 months cohort (n=940) are described in this submission.

1.3. Drug class and therapeutic indication

This is an inactivated quadrivalent influenza vaccine containing influenza haemagglutinin antigens: Type A (H1N1)-like virus; Type A (H3N2)-like virus; Type B (Victoria lineage) and Type B (Yamagata lineage). The potency of the vaccine is expressed as the concentration of HA antigen, although neuraminidase antigen is also present. The target concentration is 15 µg HA per strain.

1.4. Dosage forms and strengths

Fluarix Tetra is a quadrivalent influenza vaccine (surface antigen, inactivated) consisting of a colourless, slightly opalescent aqueous suspension packed in pre-filled syringes each containing 0.5 mL. The vaccine contains predominantly HA of four strains (2 x 'A'; 2 x 'B') of influenza virus.

1.5. Dosage and administration

Single 0.5 mL dose annually intramuscularly (IM), for the prevention of influenza caused by Influenza Virus, Types A and B, contained in the vaccine, in persons aged ≥6 months of age.

Children 6 months to less than 9 years of age who have not previously been vaccinated against influenza should receive a second dose of 0.5 ml after an interval of at least 4 weeks.

2. Background

2.1. Information on the condition being treated

Influenza, a respiratory orthomyxovirus, is a seasonal infectious disease that occurs in epidemics throughout the northern and southern hemisphere winter months, and leads to considerable morbidity and mortality globally in all age groups. Young children, particularly those younger than 2 years of age, are among the groups with the highest risk of influenza complications.¹ A meta-analysis study of 63 datasets from 42 countries showed that among children hospitalised with respiratory illness, the percentage of children with influenza varied from 5% in those <6 months, to 16% among children 5 to 17 years of age.² The pooled estimate of influenza associated hospitalisation among children <5 year was 7.4% of all respiratory hospitalisations, ranging from 4.6% (95% confidence interval [CI]: 2.8-7.4%) in the Americas to 8.5% (95% CI: 6.2-8.8%) in Southeast Asia.

Influenza A and B cause most of human disease. Influenza A viruses are divided into subtypes based on two viral external proteins, haemagglutinin (HA) and neuraminidase (NA). Of the influenza A virus subtypes, A/H3N2 and A/H1N1 subtypes are clinically the most important. Influenza type B viruses show extensive variation in antigenicity. Influenza B viruses are separated into two distinct genetic lineages, Yamagata and Victoria. In terms of infections, influenza types A viruses have been isolated from several non-human species, including birds, horses and swine whereas influenza type B viruses almost exclusively affect humans. High levels of virus type-specific antibodies are associated with protection from disease due to infections with homologous and closely related influenza virus strains.^{3,4} Novel influenza strains arise from antigenic drift due to point mutation and recombination events that occur during viral replication. These events result in the emergence of new strains of the influenza virus capable of causing epidemics, as pre-existing antibodies resulting from previous virus exposure or vaccination are generally not cross-protective.³ While influenza type A is capable of major antigenic shifts when a novel HA emerges from re-assortment with an animal influenza virus, influenza B is generally more stable. When a new subtype of influenza virus emerges, all individuals are susceptible to infection except those who have lived through earlier epidemics with a related virus subtype. Infection produces immunity to the specific virus; however, the length and extent of immunity is dependent on the degree of antigenic shift, the number of previous infections and the immune status of the individual.⁵

Influenza epidemics have been associated with the circulation of type A/H3N2, type A/H1N1 and type B viruses, either individually or together. Two genetically distinct lineages of influenza

¹ WHO Fact sheet N°211 March 2014

² Lafond KE, Nair H, Rasooly MH, et al. Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982-2012: A Systematic Analysis. *PLoS Med* 2016;13(6):e1002060.

³ Hay AJ, Belshe RB, Anderson EL, et al. Influenza viruses. In: Belshe RB, ed. *Textbook of Human Virology*. St. Louis, Missouri: Mosby Year Book, Inc, 1991;307-341.

⁴ Fiore AE, Shay DK, Broder K, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 2009 Jul 31;58(RR-8):1-52.

⁵ Beyer WE1, McElhaney J, Smith DJ, Monto AS, Nguyen-Van-Tam JS, Osterhaus AD. Cochrane re-arranged: support for policies to vaccinate elderly people against influenza. *Vaccine*. 2013 Dec 5;31(50):6030-3. Epub 2013 Oct 3.

B viruses have co-circulated since 1985.⁶ The burden of infection is largely on school age children, young adults, and the elderly.⁷ In the US, B viruses account for 24% of positive specimens and 34% of reported paediatric influenza deaths⁸, however the incidence can vary dramatically between influenza seasons (range 1%-60%).⁹ The burden of influenza B appears to be the highest for children and young adults with a relative high incidence as compared to the type A strains.^{10,11} Influenza B causes morbidity and mortality in all age groups, however in children it appears to be a disproportionate cause of influenza related hospitalisations and deaths compared to the type A strains.¹²

2.2. Current treatment options

According to the WHO, annual influenza vaccination is currently the most effective means of controlling influenza and preventing its complications, including mortality.¹³ Children also play an important role in the spread of the disease¹⁴ and immunizing young children against influenza contributes to the protection of the overall community as a result of 'herd immunity'.¹⁵

In summary, the WHO considers children 6 to 59 months of age as a risk group for seasonal influenza.¹⁶ Hence, routine annual influenza vaccination for all persons ≥ 6 months of age who do not have contraindications is recommended in the US and Canada in the universal mass vaccination programme.^{17,18} In the UK, seasonal influenza vaccination is recommended for all children aged 2-17 years.¹⁹ Extending the age indication of Fluarix Tetra to ≥ 6 months will, therefore, contribute to meet the medical need for influenza prevention through vaccination in the 6 to 35 months age group.

⁶ Rota PA, Wallis TR, Harmon MW, Rota JS et al. Cocirculation of two distinct evolutionary lineages of influenza type B virus since 1983. *Virology* 1990 Mar; 175(1):59-68.

⁷ Belshe, RB. The need for quadrivalent vaccine against seasonal influenza. *Vaccine* 2010 Sep 7; 28 Suppl 4: D45-53.

⁸ Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. *Hum Vaccin Immunother* 2012; 8(1):81-8.

⁹ www.euroflu.org

¹⁰ Grant KA, et al. High proportion of influenza B characterises the 2008 influenza season in Victoria. *Commun Dis Intell Q Rep* 2009;33(3):328-36.

¹¹ Olson DR, et al. Monitoring the impact of influenza by age: emergency department fever and respiratory complaint surveillance in New York City. *PLoS Med* 2007;4(8):e247.

¹² Thompson WW, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;8;289(2):179-86.

¹³ Barr IG, McCauley J, Cox N et al. 2010 Epidemiological, antigenic and genetic characteristics of seasonal influenza A(H1N1), A(H3N2) and B influenza viruses: Basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009–2010 Northern Hemisphere season. *Vaccine* 28 (2010); 1156-1167.

¹⁴ Brownstein JS, Mandl KD. Pediatric population size is associated with local timing and rate of influenza and other acute respiratory infections among adults. *Ann Emerg Med*. 2008; 52: 63-8

¹⁵ Loeb, M, Russell, ML, Moss L et al. Effect of Influenza Vaccination of Children on Infection Rates in Hutterite Communities. *JAMA*, 2010; 303(10): 943-950

¹⁶ WHO. *Wkly Epidemiol Rec* 2012; 47: 461–76.

¹⁷ ACIP. *Morb Mortal Wkly Rep* 2013; 62: 1–43.

¹⁸ Canada NACI 2014. PHAC NACI Advisory Committee Statement on Seasonal Influenza Vaccine 2014-2015.

¹⁹ JCVI 2013. Draft Minutes of June 2013 Meeting. Available at: <https://www.gov.uk/government/policy-advisory-groups/joint-committee-on-vaccinationand-immunisation> [accessed August 2016]

2.3. Clinical rationale

The clinical rationale is outlined above in sections 2.1 and 2.2. In summary, the WHO considers children 6 to 59 months of age as a risk group for seasonal influenza.²⁰ Hence, routine annual influenza vaccination for all persons ≥ 6 months of age who do not have contraindications is recommended in the US and Canada in the universal mass vaccination programme.^{21,22} In the UK, seasonal influenza vaccination is recommended for all children aged 2-17 years.²³ Extending the age indication of Fluarix Tetra to ≥ 6 months will, therefore, contribute to meet the medical need for influenza prevention through vaccination in the 6 to 35 months age group.

2.4. Formulation

2.4.1. Formulation development

Each 0.5 mL vaccine dose contains 15 μg HA of each of four influenza strains in phosphate buffered saline. The vaccine preparation also contains polysorbate 80, octoxinol 10, α -tocopheryl hydrogen succinate, sodium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride hexahydrate, water for injections. Residual amounts of ovalbumin $\leq 0.05 \mu\text{g}$ and formaldehyde $\leq 5 \mu\text{g}$, but also traces of gentamicin sulphate, hydrocortisone, and sodium deoxycholate from the manufacturing process may be present. The type and amount of viral antigens in Fluarix Tetra conform to the annual requirements of the Australian Influenza Vaccine Committee and the New Zealand Ministry of Health.

2.4.2. Excipients

All excipients used in the manufacture of Fluarix Tetra are in compliance with the BP and/or Ph. Eur. and/or USP monographs. The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product. Fluarix Tetra meets the WHO requirements for biological substances and influenza vaccines and the European Pharmacopoeia requirements for influenza vaccines.

2.5. Regulatory history

2.5.1. Australian regulatory history

The clinical development plan for adults and children has been designed according to the guideline for new vaccines (EMA/CHMP/VWWP/164653/2005), which has been adopted by the TGA. Fluarix Tetra is approved in children aged ≥ 3 years of age and adults.

2.6. Evaluator's commentary on the background information

This background information provides the rationale for this product including why the sponsor is seeking extension of its use to children aged ≥ 6 months of age.

²⁰ WHO. Wkly Epidemiol Rec 2012; 47: 461–76.

²¹ ACIP. Morb Mortal Wkly Rep 2013; 62: 1–43.

²² Canada NACI 2014. PHAC NACI Advisory Committee Statement on Seasonal Influenza Vaccine 2014-2015.

²³ JCVI 2013. Draft Minutes of June 2013 Meeting. Available at: <https://www.gov.uk/government/policy-advisory-groups/joint-committee-on-vaccinationand-immunisation> [accessed August 2016]

2.7. Scope of the clinical dossier

The submission contained the following clinical information:

- *Pivotal:* D-QIV-004 (115345): A Phase III, observer-blind, randomised, multi-country, non-influenza vaccine comparator-controlled study to demonstrate the efficacy of GlaxoSmithKline Vaccines' quadrivalent seasonal influenza candidate vaccine GSK2321138A (Fluarix Tetra), administered intramuscularly in children 6 to 35 months of age.
- *Supporting:* D-QIV-009 EXT 004 (116023) A phase III, open-label, multicentre study to evaluate the immunogenicity, safety and reactogenicity of a revaccination dose of GlaxoSmithKline Vaccines' quadrivalent seasonal influenza candidate vaccine Fluarix Tetra administered to children who previously participated in study D-QIV-004 (115345).
- *Supporting:* D-QIV-015 (201251) (6 to 35 months cohort). A Phase III, double-blind, randomized, multicentre study to assess safety and immunogenicity of GlaxoSmithKline Biologicals' Quadrivalent Split Virion Influenza Vaccine (GSK2321138A), Fluarix Tetra, manufactured with a new process, in adults aged 18 to 49 years and in children aged 6 months to 17 years. This study is currently in review by the TGA [for another submission].

Study D-QIV-015 was included in this submission to support extrapolation of Study D-QIV-004 and Study D-QIV-009 study data generated with Fluarix Tetra manufactured according to the previous process (licensed process [LP] at the time studies -004 and -009 were conducted), to Fluarix Tetra manufactured according to the new harmonised process (investigational process (IP) at the time of the studies, but is now the licensed process having replaced the previous process) in children 6 to 35 months of age.

2.8. Paediatric data

This application seeks to extend the indication for use of Fluarix Tetra to children aged 6 months of age or older.

2.9. Good clinical practice

Approvals to undertake the clinical studies were obtained from appropriately constituted institutional ethics committees/independent research boards, in accordance with the relevant national guidelines and regulations applicable. The studies presented in this application were conducted in accordance with GCP.

2.10. Evaluator's commentary on the clinical dossier

The main objectives of the quadrivalent paediatric clinical development programme was to demonstrate that the candidate quadrivalent influenza vaccine was effective, immunogenic and safe in children aged 6 months of age or older.

3. Pharmacokinetics (PK)

With respect to the nature of the product, clinical pharmacology data have not been assessed. The constituents of the vaccine itself are phagocytosed at the site of injection. Therefore, specific interaction or PK studies have not been carried out in man.

4. Immunogenicity

Clinical efficacy/immunogenicity and safety data arising from the pivotal study (D-QIV-004) is summarised in Section 6.0 and Section 7.0 respectively of this application.

5. Dosage selection for the pivotal studies

The dose of Fluarix Tetra used in the pivotal paediatric Study D-QIV-004 was the same as that approved for use in the current indication of children from 3 years of age and adults that is, single dose of 0.5 mL IM.

6. Clinical efficacy

In most influenza vaccine studies the derived immunogenicity data (for example HI titre) is used as a surrogate for clinical efficacy. However, in the pivotal Study D-QIV-004, the study was designed as a true clinical endpoint study, powered to assess the protection offered by Fluarix Tetra against PCR proven influenza virus infection; with changes in HI titres captured as secondary immunogenicity endpoints in a subset of participants.

6.1. Studies providing evaluable efficacy data

These include the pivotal study D-QIV-004 (115345). Supporting efficacy data was provided by D-QIV-009 EXT 004 (116023) and D-QIV-015 (201251) (6 to 35 months cohort).

6.2. Pivotal or main efficacy studies

6.2.1. Study 115345 (D-QIV-004 PRI): A Phase III, observer-blind, randomised, multi-country, non-influenza vaccine comparator-controlled study to demonstrate the efficacy of GlaxoSmithKline Vaccines' quadrivalent seasonal influenza candidate vaccine GSK2321138A (Fluarix Tetra), administered intramuscularly in children 6 to 35 months of age.

6.2.1.1. Study design, objectives, locations and dates

Study design: The objectives of this Phase III efficacy study was to demonstrate the efficacy of the Fluarix Tetra vaccine versus non-influenza vaccine controls in the prevention of RT-PCR confirmed moderate-to-severe influenza A and/or B disease and any influenza A and/or B disease in children aged 6 to 35 months of age. Participants were randomised 1:1 between Fluarix Tetra and the control group (receiving a licensed pneumococcal polysaccharide conjugated vaccine in children aged <12 months or a licensed inactivated hepatitis A vaccine /a licensed varicella virus vaccine in children ≥12 months).

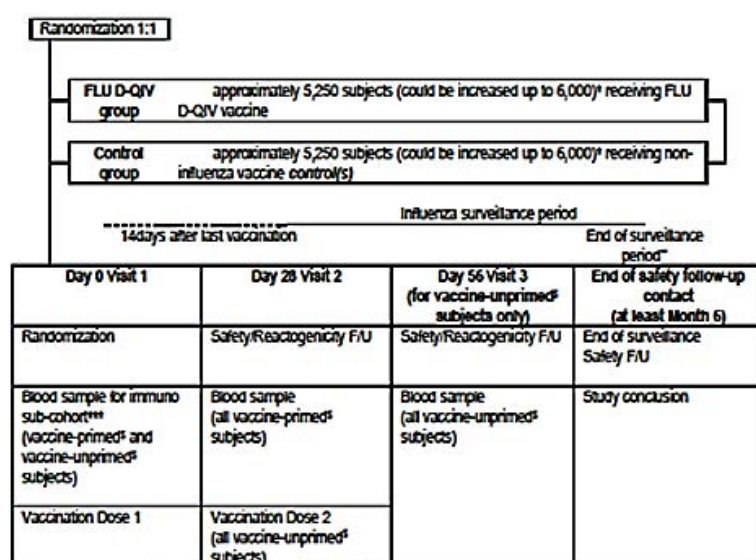
Vaccine un-primed subjects (= have not previously received at least 2 doses of seasonal influenza vaccine, separated by 28 days or more) received 2 doses of Fluarix Tetra or non-influenza vaccine control at an approximately 28 day interval. Giving 2 doses approximately one month apart is standard practice for all inactivated influenza vaccines given to this age group if they are receiving influenza vaccination for the first time, in most countries where vaccinations are recommended for healthy children or children with underlying disease. All eligible children below 12 months will be considered as vaccine un-primed. All children aged <12 months in the control group will receive two doses of pneumococcal polysaccharide conjugate vaccine (Prevenar13) at Day 0 and Day 28 during the study. An additional dose of Prevenar13 will be given after study completion. In countries with recommendation for universal vaccination

against pneumococcal infection during first year of life, the enrolment in the study will be limited by age group from ≥ 12 months.

Vaccine primed subjects (= have previously received at least 2 doses of seasonal influenza vaccine, separated by 28 days or more) were to receive a single dose of Fluarix Tetra, or one dose of non-influenza vaccine control. Vaccine primed subjects aged ≥ 12 months in the control group were to receive one dose of Hepatitis A vaccine (Havrix) as a non-influenza vaccine control and an additional booster dose of this vaccine after study completion. Vaccine unprimed subjects ≥ 12 months of age (with respect to 2-dose influenza vaccination) in the control group were to receive one dose of Havrix at Day 0 and one dose of a varicella vaccine at Day 28 during the study. A booster dose of Havrix and, if applicable, one dose of the varicella vaccine was to be given after study completion.

This design (Figure 1) allows observer-blind efficacy evaluation of Fluarix Tetra versus Havrix/a varicella vaccine in subjects aged ≥ 12 months and Fluarix Tetra versus Prevenar13 in subjects aged < 12 months. As children < 12 months from the control group will receive the pneumococcal vaccine Prevenar13 which might interfere in the evaluation of Vaccine Efficacy (VE) of Fluarix Tetra in the prevention of any cause acute otitis media (AOM) and lower respiratory illness (LRI), the analysis of these parameters will be limited to children aged from 12 to 35 months. In the present study, all cases considered as a possible consequence of an influenza virus attack (for example, AOM or LRI) will be collected independently of ILI, to allow for afebrile AOM.

Figure 1: Study design of D-QIV-004



An operational study design is presented in [APPENDIX A](#).

[†] Approximately 10,500 subjects (could be increased up to 12,000) will be enrolled (half of the subjects in the FLU D-QIV group and half of the subjects in the control group) in at least 4 independent cohorts to ensure the required number of cases of RT-PCR confirmed influenza disease (any and moderate to severe) due to seasonal strains is reached for the event-triggered analysis.

^{**} The date of the end of the influenza surveillance period for cohort 1 and 2 was end of April 2012 and end of October 2012 respectively, for cohort 3 is anticipated to be end of April 2013, for cohort 4 is anticipated to be end of October 2013. For additional cohorts, surveillance will end with the anticipated end of the regional influenza season. However, the central GSK team may decide to modify the influenza surveillance period depending on the course of the influenza season in the participating countries.

^{***} The immuno sub-cohort will include approximately 600 subjects from cohorts 1 and 2 (approximately 400 subjects in the FLU D-QIV group, approximately 200 subjects in the control group) and approximately 150 subjects (half of the subjects from the FLU D-QIV group and half of the subjects from the control group) from cohort 3. In addition, up to 50 subjects per participating country (half of the subjects from the FLU D-QIV group and half of the subjects from the control group) from cohort 4 and any additional cohort will be included in the immuno sub-cohort. Subjects participating in the immuno sub-cohort will be enrolled in pre-specified centers.

6.2.1.2. Co-Primary objective(s)

- To evaluate the efficacy of Fluarix Tetra in the prevention of RT-PCR confirmed moderate-to-severe influenza (Table 1) A and/or B disease due to any seasonal influenza strain, when compared to non-influenza vaccine controls in children aged 6 to 35 months;

Criterion to be used for this co-primary objective

The efficacy of the Fluarix Tetra vaccine will be demonstrated if the LL of the two-sided 97.5% CI for VE is >25%

2. To evaluate the efficacy of Fluarix Tetra in the prevention of RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain when compared to non-influenza vaccine controls in children aged 6 to 35 months.

Criterion to be used for this co-primary objective

The efficacy of the Fluarix Tetra vaccine will be demonstrated if the LL of the two-sided 97.5% CI for VE is >15%.

6.2.1.3. Secondary objectives*Efficacy*

To evaluate the efficacy of Fluarix Tetra in the prevention of:

- LRI associated with RT-PCR confirmed influenza A and/or B, versus non-influenza vaccine controls.
- Culture confirmed moderate-to-severe influenza A and/or B disease due to antigenically-matching influenza strains when compared to non-influenza vaccine controls.
- Culture confirmed influenza A and/or B disease of any severity due to antigenically-matching influenza strains when compared to non-influenza vaccine controls.
- Culture confirmed moderate-to-severe influenza A and/or B disease due to any seasonal influenza strain, when compared to non-influenza vaccine control.
- Culture confirmed influenza A and/or B disease of any severity due to any seasonal influenza strain, when compared to non-influenza vaccine controls.
- AOM associated with RT-PCR confirmed influenza A and/or B, versus non-influenza vaccine controls.
- RT-PCR confirmed severe influenza A and/or B disease, when compared to non-influenza vaccine controls.

Immunogenicity

To evaluate the immunogenicity of Fluarix Tetra in terms of HI antibody response 28 days after completion of vaccination in an immunogenicity (immuno) sub-cohort of subjects. The immuno sub-cohort will include approximately 600 subjects from Cohorts 1 and 2 (approximately 400 subjects in the Fluarix Tetra group, approximately 200 subjects in the control group) and approximately 150 subjects (half of the subjects from the Fluarix Tetra group and half of the subjects from the control group) from Cohort 3. In addition, up to 50 subjects per participating country (half of the subjects from the Fluarix Tetra group and half of the subjects from the control group) from cohort 4 and any additional cohort will be included in the immuno sub-cohort. Standard derived variables are Geometric Mean Titres (GMTs) of HI antibody titres at Days 0 and 28/56; Seropositivity rates at Days 0 and 28/56; Seroconversion rates (SCR) at Day 28/56; Mean geometric increase (MGI) at Day 28/56; Seroprotection rates (SPR) at Days 0 and 28/56.

Key: SCR is defined as the % of vaccinees with a pre-vaccination titre <1:10 and a post-vaccination titre ≥1:40 or a pre-vaccination titre ≥1:10 and ≥four-fold increase in post-vaccination titre. MGI is defined as the fold increase in serum HI GMTs postvaccination compared to pre-vaccination. SPR is defined as the percentage of vaccinees with a serum HI titre ≥1:40 = threshold for indicating protection in adults. SPR will be also presented as the percentage of vaccines with a serum HI titre ≥1:80 and ≥1:160.

Reactogenicity/safety

- To evaluate reactogenicity of Fluarix Tetra and non-influenza vaccine controls in terms of solicited local and general adverse events (AEs) during 7 days after each vaccination and unsolicited symptoms during 28 days after each vaccination.
- To evaluate safety of Fluarix Tetra and non-influenza vaccine controls in terms of AEs with medically attended visits (MAVs), serious adverse events (SAEs) and potential Immune-Mediated-Diseases (pIMDs) during the entire study period (6-8 mths after study start).

6.2.1.4. Exploratory endpoints*Efficacy*

1. To evaluate the efficacy of Fluarix Tetra in the prevention of RT-PCR confirmed mild (= not fulfilling the definition of moderate-to-severe influenza A and/or B).
2. To evaluate the efficacy of Fluarix Tetra in the prevention of RT-PCR confirmed any disease, mild disease and moderate-to-severe disease by influenza A type, A subtype and influenza B type and B lineage.
3. To evaluate the efficacy of Fluarix Tetra in the prevention of RT-PCR confirmed any disease and moderate-to-severe influenza A and/or B disease, when compared to Non-influenza vaccine controls, by age group and vaccine-priming status.
4. To evaluate the efficacy of Fluarix Tetra, in children aged 12-35 months, during the influenza activity period in each country, when compared to non-influenza vaccine controls, in the prevention of: ILIs, AOM and LRI
5. To describe clinical symptoms / signs of RT-PCR-confirmed any, mild and moderate-to-severe influenza disease and associated day-care/school absenteeism and parent(s)/LAR(s) workdays lost, in the Fluarix Tetra and control group.
6. To evaluate health care utilization associated with RT-PCR confirmed any, mild and moderate-to-severe influenza disease in the Fluarix Tetra and control group.
7. To explore potential immunologic correlates of protection 28 days post-vaccination.

Epidemiology

1. To assess the presence of Respiratory Syncytial Virus and/or other respiratory pathogens in swabs collected at the onset of ILI/LRI/AOM episode in Fluarix Tetra and control groups
2. To explore pre-vaccination RSV seropositivity status in children in the immune sub-cohort.

Reactogenicity and Safety

Solicited local and general symptoms: Occurrence, intensity and duration of each local solicited AE and general solicited AE within 7 days (Day 0-Day 6) after each vaccination.

Unsolicited AEs: Occurrence, intensity and relationship to vaccination of unsolicited AEs within 28 days (Day 0- Day 27) after each vaccination.

AEs with MAV: Occurrence, intensity and relationship to vaccination of AEs with MAV during the entire study period.

SAEs: Occurrence and relationship to vaccination of SAEs during the entire study period.

pIMDs: Occurrence, intensity and relationship to vaccination of pIMDs during the entire study period.

Locations: n=106 in 13 countries: Bangladesh, Belgium, Czech Republic, Honduras, India Dominican Republic, Lebanon, Philippines, Poland, Spain, Thailand, Turkey, and UK.

Dates: First enrollment: 01-Oct-2011; last visit: 31-Dec-2014. Data lock point: 13-Jul-2016. Study report 05-Dec-2016, errors identified and Amended report provided 22-Feb-2017.

Protocols: Amendment 1: Final: 08-Jul-2011; Amendment 2: Final: 27-Oct-2011; Amendment 3: Final: 21-Jun-2012; Amendment 4: Final: 04-Apr-2013; Amendment 5: Final: 30-Jul-2014.

Duration of the study: For each subject, study duration was approximately 6-8 months (minimum 6 months after the first vaccination until the end of safety follow-up contact but not earlier than the end of the influenza surveillance period‡).

‡ Surveillance for ILIs and consequences of influenza virus attack was to start 14 days after last vaccination for each subject and continue until end of influenza activity period. Date of the end of surveillance was 30 Apr 2012 for all cohort 1 countries, 31 Oct 2012 for all cohort 2 countries, 30 Apr 2013 for cohort 3 countries, 31 Oct 2013 for Dominican Republic and Thailand and 15 Nov 2013 in Honduras, Bangladesh, Philippines in Cohort 4, and 31 Oct 2014 for all Cohort 5 countries.

Table 1: Definition of ‘Moderate to Severe’ and ‘Severe’ Influenza in D-QIV-004

<i>“Any” RT-PCR confirmed influenza with one or more of the manifestations below</i>	Clinical end-point category	
	Moderate to severe influenza (any criterion is sufficient)	Severe influenza (any criterion is sufficient)
Fever >39°C (any route)	X	
Physician-diagnosed AOM	X	
Physician-diagnosed pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis or croup	X	
Physician-diagnosed serious extra-pulmonary complication of influenza, including myositis, encephalitis or other neurologic condition including seizure, myocarditis / pericarditis or other serious medical condition	X	X
Hospitalisation in the Intensive Care Unit (ICU)	X	X
Supplemental oxygen requirement for >8 hrs	X	X

6.2.1.5. Inclusion and exclusion criteria

Inclusion Criteria: Subjects who the investigator believed that their parents/ legally authorised representative (LAR(s)) could and would comply with the requirements of the protocol (for example, safety reporting, reporting an ILI

or MAV which might have included using internet, being available for follow-up contacts); male or female between, and including, 6 and 35 months of age at the time of first vaccination; children were eligible regardless of history of influenza vaccination; Written informed consent obtained from the parent(s) /LAR(s) of the subject; Subjects in stable health as determined by medical history and clinical examination before entering into the study.

Exclusion criteria: Participation in a previous D-QIV-004 study (115345) cohort; Child in care; Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period; Prior receipt of any influenza vaccine (registered or investigational) within 6 months preceding the first dose of study vaccine, or planned use of such vaccines during the study period; Children with underlying illness who were at risk of complications of influenza and for whom yearly (seasonal) influenza vaccination was recommended in their respective country; Any confirmed or suspected immunosuppressive or immunodeficient condition (including HIV), based on medical history and physical examination (no lab testing required); Chronic administration (>14 days in total) of immunosuppressants or other immune modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this was to mean a dose equivalent to either ≥ 0.5 mg/kg of body weight or maximum of 10 mg/day of prednisone or equivalent. Administration of immunoglobulins and/ or any blood

products within 3 months preceding the first dose of study vaccine or planned administration during the study period; Any known or suspected allergy to any constituent of influenza vaccines (including egg), non-influenza vaccine comparators (including neomycin) and latex; a history of anaphylactic-type reaction to consumption of eggs; or a history of severe adverse reaction to a previous vaccination; Any contraindication to intramuscular injection; Acute disease and/or fever at the time of enrolment. Any other condition which in the opinion of the investigator prevented the subject from participating in the study.

Additional criteria for children ≥ 12 months of age: Prior receipt of any licensed varicella vaccine (but, for countries with varicella vaccine administered as 2-dose schedule, prior receipt of a single dose of a varicella vaccine was allowed if administered ≥ 2 weeks before the first study vaccination) or any licensed hepatitis A vaccine or planned use of these vaccines during the study period. Other routine registered childhood vaccinations were permitted; Any history of hepatitis A or varicella disease.

Additional criteria for children 6 - 11 months of age in countries without universal mass vaccination recommendation for pneumococcal vaccine: Prior receipt of any pneumococcal conjugated vaccine or planned use of this vaccine during the study period. Other routine registered childhood vaccinations were permitted.

6.2.1.6. Study treatments

Study vaccine, dose, mode of administration

- Vaccine primed subjects that are ≥ 12 months of age: one IM injection of Fluarix Tetra into the deltoid† muscle at Day 0.
- Vaccine un-primed subjects ≥ 12 months of age: two IM injections of Fluarix Tetra into the deltoid† muscle at Day 0 and at Day 28.
- Subjects < 12 months of age: two IM injections of Fluarix Tetra into anterolateral thigh.

† If muscle size was adequate, otherwise into the anterolateral area of the thigh.

Vaccine composition /dose /lot number

The Fluarix Tetra contained 60 μg HA, that is, 15 μg each of the A/H1N1, A/H3N2, B/Yamagata and B/Victoria strains in a total injected volume of 0.50 mL/dose. Strains included in the vaccines used during the different seasons in this study followed WHO recommendation. The lot nos. were DFLBA014A1 (Cohort 1), DFLBA018A (Cohort 2), DFLBA020B (Cohort 3 & 4), DFLBA021A (Cohort 4), AFLBA001A and AFLBA002AB (Cohort 5).

Control vaccines, dose and mode of administration

Four vaccines used as active non-influenza vaccine controls:

- GSK Biologicals' licensed Hepatitis A virus vaccine, Havrix; each 0.5 mL dose contained 720 EL.U. of viral antigen (Hepatitis A virus strain HM175) adsorbed onto 0.25 mg of aluminium hydroxide. The lot nos. were AHAVB525A (Cohort 1), AHAVB567D (Cohort 2), AHAVB603A (Cohort 3), AHAVB573F (Cohort 4), AHAVB675A (Cohort 5) and AHAVB761A (Cohort 5).
- GSK Biologicals' licensed varicella virus live attenuated vaccine, Varilrix; each 0.5 mL dose of Varilrix contained at least 103.3 plaque-forming units of the varicella-zoster virus. The lot nos. were AVARB356AZ (Cohort 1 & 2), AVARB396AZ (Cohort 2), AVARB413AZ (Cohort 3), AVARB447AY (Cohort 4), AVARB509AZ (Cohort 5), AVARB513AZ (Cohort 5), AVARB451AZ (Cohort 5) and AVARB495AZ (Cohort 5).
- Sanofi Pasteur MSD's licensed varicella virus live vaccine, Varivax/ProVarivax. Each 0.5 mL dose of *Varivax/ProVarivax* contained a minimum of 1350 plaque-forming units of Oka/Merck varicella virus. The lot nos. were DEXTA414AY (NPO6420)(Cohort 1), DEXTA444AY (G019895) (Cohort 3) and,

- Pfizer' licensed pneumococcal polysaccharide conjugate vaccine, Prevenar13. Each 0.5 mL dose of *Prevenar13* consisted of pneumococcal polysaccharide serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, conjugated to CRM197 carrier protein and adsorbed on aluminium phosphate (0.125 mg aluminium). The lot nos. were DEXTA407AZ (F08783) (Cohort 1 and Cohort 2), DEXTA412AZ (F14427) (Cohort 2), DEXTA424AZ (F40144) (Cohort 2), DEXTA407AX (F08783) (Cohort 3) DEXTA431AY (F54377) (Cohort 3 and Cohort 4), DEXTA472AZ (G59985) (Cohort 4), and DEXTA492AZ (H07583) (Cohort 5).

Table 2: Study treatment schedule in D-QIV-004

Study groups	Treatment	Age (Min/Max) (months)	Number of subjects [†]	Epochs
				Primary epoch :
FLU D-QIV	FLU D-QIV at Day 0 [‡]	12-35 (primed)	approximately 5,250 †	X
	FLU D-QIV at Day 0 and Day 28 [‡]	6-35 (unprimed)		
Control group	Prevenar13 at Day 0 and Day 28 [‡]	6-11 (unprimed)	approximately 5,250 †	X
	Havrix at Day 0 [‡]	12-35 (primed)		
	Havrix at Day 0 and Varivax at Day 28** (or Varivax/ProVarivax at Day 28***)	12-35 (unprimed)		

†. Sample size will be driven by the accrual of cases.

‡ Could be increased up to 6,000 subjects per group

§. In all participating countries.

¶. In countries without recommendation for universal vaccination against pneumococcal infection during first year of life, where *Prevenar13* is licensed.

** In countries where *Varivax* is licensed and selected for the study.

*** In countries where *Varivax/ProVarivax* is licensed and selected for the study.

Table 3: Overview of strains included in the influenza vaccines – pivotal Study D-QIV-004

D-QIV-004	Study Cohort				
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Countries	Belgium, Czech Republic, Poland, Spain, UK	Bangladesh, Dominican Republic, Honduras	Belgium, Czech Republic, Lebanon, Poland, Spain, Turkey, UK	Bangladesh, Dominican Republic, Honduras, Philippines, Thailand	Bangladesh, Dominican Republic, Honduras, India, Philippines, Thailand
Vaccination season	2011-2012	2012	2012-2013	2013	2014
	Strains included in the vaccine				
Flu A (H1N1) HI	A/California/7/2009*	A/California/7/2009†	A/Christchurch/16/2010†	A/Christchurch/16/2010†	A/Christchurch/16/2010†
Flu A (H3N2) HI	A/Victoria/210/2009*	A/Victoria/210/2009†	A/Victoria/361/2011†	A/Victoria/361/2011†	A/Texas/50/2012†
Flu B (Victoria) HI	B/Brisbane/60/2008*	B/Brisbane/60/2008†	B/Brisbane/60/2008†	B/Brisbane/60/2008†	B/Brisbane/60/2008†
Flu B (Yamagata) HI	B/Brisbane/3/2007**	B/Hubei-Wujiagang/158/2009†	B/Hubei-Wujiagang/158/2009†	B/Hubei-Wujiagang/158/2009†	B/Massachusetts/2/2012†

* Recommended WHO composition for 2011-2012 season quadrivalent vaccine

** Yamagata lineage added to the composition

† Recommended WHO composition for 2012-2013, 2013-2014 seasons quadrivalent vaccine

NOTE: The A/H1N1 strains, A/California/7/2009 and A/Christchurch/16/2010, were antigenically similar, i.e. A/California/7/2009-like

6.2.1.7. Efficacy variables and outcomes

Clinical efficacy variables definitions for the investigator's judgement

- *ILI* defined by a) temperature $\geq 38.0^{\circ}\text{C}$ (any route) and b) at least one of the following: cough, runny nose, nasal congestion or breathing difficulty.
- *LRI* include cases of physician-diagnosed pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis and croup.
- *AOM*: include cases of physician-diagnosed otitis media.

Definitions for statistical analysis purposes

- *Validated AOM*: defined as a visually abnormal tympanic membrane suggesting an effusion in the middle ear cavity (as per a physician's judgment), concomitant with at least one of the following signs and/or symptoms of acute infection: fever (temperature of $\geq 37.5^{\circ}\text{C}$, by any route), earache, irritability, diarrhoea, vomiting, acute otorrhoea, or other symptoms of respiratory infection.
- *Recurrent AOM* was defined as three or more distinct and well documented episodes of AOM, as recorded in the medical history of the subject.
- *RT-PCR confirmed influenza disease*: An episode of ILI or a consequence of influenza virus attack (for example, AOM or LRI), occurring after the administration of the study vaccine during the influenza surveillance period for which a nasal swab specimen yields influenza virus A and/or B by RT-PCR analysis.
- *Culture-confirmed influenza disease*: An episode of ILI or a consequence of influenza virus attack (for example, AOM or LRI), occurring after the administration of the study vaccine during the influenza surveillance period for which a nasal swab specimen yields influenza virus A and/or B by viral culture analysis.
- *Moderate-to-severe influenza* and *severe influenza* are a subset of 'any' RT-PCR confirmed influenza disease
- *Health care utilization*: hospitalisation, emergency care visit, visit to or by medical specialist, unscheduled or scheduled visit to or by General Practitioner / Paediatrician, use of antibiotics (orally or parenteral), antipyretics and antiviral therapy, linked to the ILI episode, AOM or LRI.
- *Duration of ILI/LRI-episode*: from the first day with fever (temperature of $\geq 38.0^{\circ}\text{C}$, by any route) and at least one respiratory symptom (cough, runny nose, nasal congestion or breathing difficulty) until the event resolution defined as the first day when the following conditions were met simultaneously: temperature $\leq 37.5^{\circ}\text{C}$ with no fever reducers used, other symptoms (cough, runny nose / nasal congestion, vomiting and feels unwell) either absent or mild, and a return of the child to normal activities. If fever (temperature of $\geq 38.0^{\circ}\text{C}$, by any route) reappeared or other symptoms (cough, runny nose, nasal congestion or breathing difficulty) worsened to moderate or severe levels within 7 days after ILI onset, the duration of the episode was to be calculated until the first time that the above listed conditions were met after worsening of these symptoms. In this case, the investigator was to judge if the previous episode had resolved and this event was to constitute a new episode.
- *Duration of AOM*: from first day of otitis symptoms until resolution defined as first day when the following conditions were met simultaneously: temperature $\leq 37.5^{\circ}\text{C}$ with no fever reducers used, other symptoms (ear tugging, increasing crying, fussiness, disturbed sleep, decreased play and eating less) absent or most of them absent with a maximum of 2 of them qualified as mild. A new episode was only to be taken into account after the resolution of the previous one, as judged by the investigator.
- *Attendance to Day care centre/school* was defined as exposed to 3 or more nonfamily members <5 years for at least 10 hours a week.

Methods used to evaluate immunogenicity/efficacy

Viral RNA isolated from nasal swabs was amplified and subjected to quantitative RT-PCR identification of influenza A or B. Influenza A confirmed samples were subjected to further RT-PCR characterisation to sub-classify into A/H1N1 or A/H3N2 strains. Influenza B confirmed samples were subjected to further RT-PCR characterisation. However, an additional DNA sequencing step was needed to further classify into B/Victoria or B/Yamagata lineages, since the two B lineages could not be distinguished by sizing alone. Nasal swabs confirmed for the

presence of influenza A or B by RT-PCR were sent to Quest laboratory for viral culture confirmation (secondary efficacy endpoint) of influenza A and or B by immunostaining. An aliquot of each sample confirmed for the presence of influenza A or B by RT-PCR (regardless of cell culture results), was forwarded [information redacted] for antigenic characterisation. Viral supernatant samples received from Quest were independently expanded in viral cultures and then subjected to antigenic characterisation (secondary efficacy endpoint). The results of RT-PCR/sequencing for A strain type and B lineage sub-classification were used to determine which specific antigenic assay had to be performed by [information redacted] for a given sample. Therefore, samples identified as A/H1N1 or A/H3N2 by RT-PCR were then assessed for antigen characterisation using A/H1N1 HI assay or A/H3N2 Virospot MN assay, respectively. Similarly, samples identified as B/Victoria or B/Yamagata by RTPCR/ sequencing were then assessed for antigen characterisation using B/Victoria HI assay or B/Yamagata HI assay, respectively. For each of the A and B lineage strains, the results were reported as either 'vaccine strain matched' or 'vaccine strain non-matched.' Note that samples that were negative for either influenza A or B culture confirmation by immunostaining (at Quest), could contribute to the cell culture confirmed endpoint if viral culture supernatants reached a significant virus titre to be evaluated with antigenic typing assay. For example, the following decision algorithm would be used to identify a sample as A/H1N1 (similarly for A/H3N2, B/Victoria, or B/Yamagata):

Sample identified as culture-confirmed *vaccine matched* A/H1N1 strain:

- RT-PCR confirmed as A/H1N1,
- Culture confirmed as A or negative at Quest (immunostaining), and
- Identified by antigenic characterisation as vaccine-matched A/H1N1.

Sample identified as culture-confirmed *vaccine non-matched (drifted)* A/H1N1 strain:

- RT-PCR confirmed as A/H1N1, culture confirmed as A or negative confirmation at Quest (immunostaining), and
- Identified by antigenic characterisation as vaccine non-matched for A/H1N1.

Table 4 summarises the methods for influenza detection and typing from nasal mucus swabs, conducted at a GSK Biologicals laboratory or validated lab designated by GSK Biologicals.

Table 4: Influenza detection, typing and viral culture

Component	Method	Measure	Laboratory
Influenza Virus A or B	Quantitative Reverse Transcription - Polymerase Chain Reaction (RT-qPCR)	Presence or Identity	GSK Biologicals
Influenza Virus AH1N1.RNA	Reverse Transcription -Polymerase Chain Reaction (RT-PCR) Typing	Presence or Identity	GSK Biologicals
Influenza Virus AH3N2.RNA	Reverse Transcription -Polymerase Chain Reaction (RT-PCR) Typing	Presence or Identity	GSK Biologicals
Influenza Virus B.RNA	Reverse Transcription -Polymerase Chain Reaction (RT-PCR) Typing and sequencing	Presence or Identity	GSK Biologicals
Influenza Virus A or B	Viral culture	Presence or Identity	Quest (or Viroclinics*)
Influenza Virus A (H1)	HI method for antigen typing	Match or no match	Viroclinics
Influenza Virus A (H3)	Microneutralisation Assay for antigen typing	Match or no match	Viroclinics
Influenza Virus B	HI method for antigen typing	Match or no match	Viroclinics

*Viral culture samples that were negative by immunostaining at Quest, but determined as either vaccine-matched or non-matched at Viroclinics were classified as 'culture-confirmed'

Quantitative RT-qPCR assay for influenza detection

Viral RNA from 200 mL of the clinical sample extracted using the MagNA Pure LC Instrument and MagNA Pure LC Total Nucleic Acid Isolation Kit. Purified RNA eluted in a final volume of 50mL. RNA from the clinical sample amplified and detected using the specific primers and

probes (designed in the Matrix gene) for FLU-A and FLU-B RNA with the help of ABI PRISM 7900 HT Sequence Detection System 96-Well Block Module (Applied Biosystems). Viral load values quantified and the sample considered positive when the viral load was equal to or above the assay cut-off set at the limit of detection. Several standard control steps used to monitor any potential contamination.

Viral culture confirmation (immunostaining for influenza A and B)

One Rhesus Monkey Kidney and one Madin-Darby Canine Kidney (MDCKSIAT1) tissue culture were inoculated with approximately 0.3 mL of nasal swab specimens confirmed influenza A or B by RT-PCR positive. Tissue cultures incubated at 33-36°C for up to 2 weeks followed by examination for cytopathic effects. If a CPE was observed, a slide was prepared for staining with anti-influenza A and B fluorescent antibodies and read under a fluorescent microscope. Positive/negative influenza A/B isolation was then recorded.

Antigenic influenza strain typing methodology (from viral culture supernatants)

The MDCK-STAT1/RMK culture supernatants of specimens found positive by RT-PCR were transferred from [information redacted] and further evaluated. [information redacted] performed three culture amplifications of the virus on MDCK cells to generate sufficient material for the subtyping assays. A/H1N1, B/Victoria and B/Yamagata antigenic typing done with the HI assay. The conventional HI assay could not be used for influenza A/H3N2 strain typing due to emergence of H3N2 strains with impaired haemagglutination phenotype during the study. An alternative assay was developed and validated for A/H3N2 strain typing. This new method was based on an MN assay revealed with an NP-antibody = Virospot MN assay. Details of the standard operating procedures and validation reports for the efficacy assays performed in D-QIV-004 were provided.

Haemagglutination inhibition assay

HI antibodies measured on thawed frozen serum samples in paired serum specimens using WHO and CDC endorsed methods. Subjects with titres below detection (1:10) = seronegative, those with demonstrable titre ($\geq 1:10$) = seropositive. A titre $\geq 1:40$ to a specific influenza virus strain is considered 'seroprotective' that is, may be associated with up to 50% protection against influenza disease due to the same virus strain, relative to a titre $< 1:10$.

Microneutralisation assay

The 50% neutralisation titre of a serum was calculated as the GMT between the highest serum dilution able to totally neutralise the virus and the next serum dilution where viruses remained detectable. Each serum sample was tested once. The assay cut-off values for each specific strain were provided.

Neuraminidase inhibition assay

Determined using an enzyme-linked lectin assay. The NI titre of a serum was measured by mixing a fixed amount of neuraminidase with serial dilutions of serum and was set as the reciprocal of the serum dilution reducing the colorimetric signal resulting from desialylation by 50%. The assay cut-off values used for each specific strain were provided.

6.2.1.8. Randomisation and blinding methods

Randomisation

Subject numbers assigned sequentially. The randomisation was performed at GSK Biologicals, Belgium, using MATEX, a program developed for use in SAS® (Cary, NC, US) by GSK Biologicals. The enrolment was to be performed to ensure the distribution of the population across the three age groups (6-11 months, 12-23 months, and 24-35 months). The treatment allocation at the investigator site was performed using a central randomisation system on internet. The treatment numbers were to be allocated by dose. The randomisation algorithm was to use a

minimisation procedure accounting for: country, centre, age, prior influenza vaccine priming status, attendance to day-care centre/school (defined in the protocol), history of recurrent AOM (≥ 3 or more distinct and well documented episodes) and history of vaccination with conjugated pneumococcal vaccine (≥ 3 doses). Minimisation factors had equal weight in the minimisation algorithm. Subjects were enrolled into the immune sub-cohort from pre-defined centres. For Cohorts 1 and 2 the subjects were enrolled into the Fluarix Tetra and control groups with a ratio of 2:1, for Cohorts 3 and 4 this ratio was 1:1. A balanced distribution between treatment groups and across the two age groups (6 - 23 months and 24 - 35 months) for the entire immuno sub-cohort was managed using SBIR application.

Blinding

Data was collected in an observer-blind manner that is, the parent(s)/LAR(s) or guardian, and those responsible for the evaluation of any study endpoints (for example, safety, reactogenicity and efficacy) were all unaware of which vaccine was administered. This was achieved by vaccine preparation and administration by authorised medical personnel who did not participate in any of the study clinical evaluation assays. In addition, serological data were only made available at the end of the study, to avoid inadvertent unblinding.

6.2.1.9. Analysis populations

In D-QIV-004, subjects aged 6 to 35 months were enrolled in 5 independent cohorts over 5 influenza seasons to ensure the required number of cases of RT-PCR confirmed influenza disease due to seasonal strains (Table 3). In all studies, the TVC included all subjects with at ≥ 1 vaccine administration documented. In D-QIV-004 an According-to-protocol cohort for analysis of efficacy (ATP-E) and an ATP-E - Time to event were defined. The ATP-E cohort included all eligible subjects from the TVC, who met all inclusion and exclusion criteria, who had received study vaccine(s) according to their random assignment, for whom the administration site of the study vaccine was known, who had not received any non-protocol influenza vaccine during the relevant analysis interval, who had not received any investigational or nonregistered product other than the study vaccine during the relevant analysis interval, for whom the randomisation code had not been broken or for whom inadvertent unblinding had not occurred, who started their influenza surveillance period, who did not meet any of the criteria for elimination from an ATP analysis during the study and who had a swab collected during the window (0-7 days) of episode onset. The ATP-E - Time to event cohort used the same elimination criteria as for the ATP-E cohort to include all eligible subjects. But, the only difference was subjects were censored as of the date that they met any of the censoring criteria pre-defined in the SAP (for example, subjects who received a vaccine or medication forbidden in the protocol or for whom the randomisation code was broken) before occurrence of the first clinical vaccine efficacy endpoint event. In all studies, an ATP cohort (sub cohort in D-QIV-004) for analysis of immunogenicity was defined and included all eligible subjects from the TVC who met the inclusion and exclusion criteria, did not meet a criterion for elimination/exclusion from an ATP analysis and with immunogenicity endpoint measures available for ≥ 1 study vaccine strain.

6.2.1.10. Sample size

GSK calculated the initial sample size for the study based on true efficacy assumptions of 40%. A recent study²⁴ demonstrated 43% (95% CI, 15-61) efficacy of European licensed TIVs against PCR-confirmed influenza in 6 month to <72 month old children. With a 1:1 allocation between Fluarix Tetra and control group, and an assumed true VE of 40%, approximately 536 RT-PCR confirmed influenza cases due to influenza A and B strains were needed to demonstrate with 90% power that the LL of the two-sided 95% CI for the VE is $>20\%$. Considering a conservative influenza virus attack rate of 9% in the control group, and an estimated 10% non-

²⁴ Vesikari T, et al. Efficacy of an MF59®-Adjuvanted Seasonal Influenza Vaccine Versus Non-Adjuvanted Influenza Vaccine and Control Vaccine In 6-<72 Month Old Children.

evaluable subjects, approximately 8,200 subjects (4,100 per treatment group) needed to be recruited to reach the required number of cases of RT-PCR confirmed influenza illness due to influenza A/B strains. Acquisition of new data in a paediatric population (children from 3-8 years old) originating from an efficacy trial using GSK's Q-QIV vaccine offered the opportunity to validate the use of moderate-to-severe influenza disease as a meaningful clinical endpoint for the D-QIV-004 study. Assuming a true VE of 55% against RT-PCR confirmed moderate-to-severe influenza A and/or B disease, 240 cases will be needed to demonstrate with 93% power that the LL of the two-sided 97.5% CI of Fluarix Tetra efficacy is >25%; assuming a true VE of 35% against any RT-PCR confirmed influenza A and/or B disease, 702 cases will be needed to demonstrate with 90% power that a LL of the two-sided 97.5% CI of Fluarix Tetra efficacy is >15%.

Considering occurrence of RT-PCR confirmed moderate-to-severe influenza cases of 3.5% in the control group, occurrence of RT-PCR confirmed influenza of any intensity of 9% in the control group, and an estimated 10% non-evaluative subjects, approximately 10,500 subjects with a maximum of 12,000 subjects (approximately 5,250 per treatment group with a maximum of 6,000 per group) will be recruited into additional independent cohorts to reach the required number of cases. The analysis of efficacy was to be event-driven, with at least 255 and 744 cases of moderate-to-severe disease and any intensity disease respectively, confirmed by RT-PCR due to any seasonal strain, to ensure achieving at least 240 cases of moderate-to-severe RT-PCR confirmed influenza disease and at least 702 cases of RT-PCR confirmed influenza disease (any) in the according-to-protocol cohort. Cohort 1: In the Northern Hemisphere (NH), recruitment started Oct 2011 and 1777 subjects were to be recruited; Cohort 2: In subtropical countries, recruitment started Apr 2012 and 2539 subjects were to be recruited; Cohort 3: In the NH, recruitment started in Oct 2012 and 1564 subjects were to be recruited; Cohort 4 and additional independent cohorts: Additional subjects (up to 12,000) will be recruited to reach the required number of cases of RT-PCR confirmed influenza disease (any and moderate to severe) for the event-triggered analysis. This might include NH countries end of 2013 and subtropical countries beginning of 2014 to reach the required number of events to trigger the analysis.

6.2.1.11. Statistical methods

Analysis of demographics/baseline characteristics

Cohorts for analysis and withdrawal status were summarised overall and per group. The distribution of subjects among study centres was tabulated as a whole and per group and classified subjects into disposition categories, including subjects who entered, completed, or withdrew from the study. Demographic characteristics at first vaccine dose of each study cohort and living environment parameters (day care utilisation, family situation and exposure to passive smoking) were tabulated overall and per group. History of influenza and pneumococcal vaccination since birth and history of recurrent AOM were tabulated overall and per group. Demographic characteristics at first vaccine dose were presented by age category, priming status, geographical ancestry, gender, country and cohort.

Analysis of efficacy

The primary analysis and all confirmatory VE analyses were based on the according-to-protocol efficacy (ATP-E) - Time to Event cohort. All descriptive efficacy tables were based on the ATP-E cohort. A secondary analysis based on the TVC was performed to complement the ATP analysis. The time-to-event methodology based on a proportional hazard model was used for all vaccine efficacy analyses. Diagnostics were performed to check whether the assumption of proportionality was fulfilled. In case of evidence that this assumption wasn't satisfied, a non-parametric analysis was done.

Analysis of primary efficacy endpoints

Attack rates and VE with 97.5% CI were tabulated for primary efficacy endpoints and the pre-specified statistical success criteria used for evaluation of the end-points were:

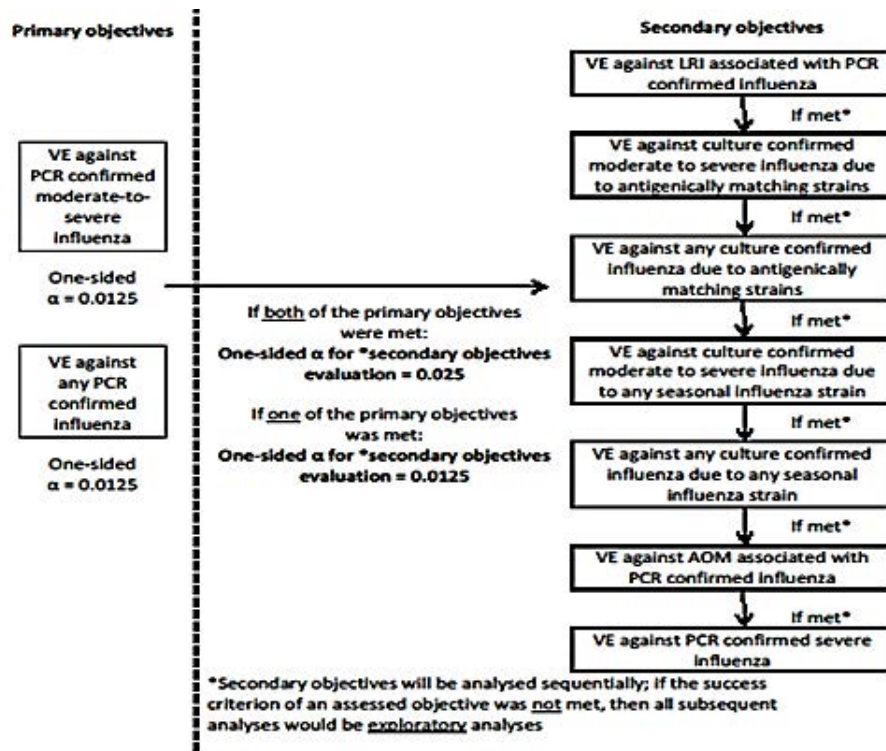
-
- The efficacy of Fluarix Tetra in protecting against RT-PCR confirmed moderate-to-severe influenza disease due to any seasonal strain of influenza A and/or B was demonstrated if the LL of the two-sided 97.5% CI of VE was >25%.
 - The efficacy of Fluarix Tetra in protecting against RT-PCR confirmed influenza disease of any severity due to any seasonal strain of influenza A and/or B was demonstrated if the LL of the two-sided 97.5% CI of VE was >15%.

Analysis of secondary efficacy endpoints

The secondary efficacy objectives were evaluated sequentially with an alpha level of 2.5% (one-sided or 95% CI). The pre-specified statistical success criteria were:

- The efficacy of Fluarix Tetra in protecting against LRI associated with RT-PCR confirmed influenza A and/or B infection was demonstrated if the LL of the two-sided 95% CI of VE was >15%.
- The efficacy of Fluarix Tetra in protecting against culture-confirmed moderate-to-severe influenza A and/or B disease due to antigenically matching influenza strains was demonstrated if the LL of the two-sided 95% CI of VE was >15%.
- The efficacy of Fluarix Tetra in protecting against any culture-confirmed influenza A and/or B disease due to antigenically matching influenza strains was demonstrated if the LL of the two-sided 95% CI of VE was >15%.
- The efficacy of Fluarix Tetra in protecting against culture-confirmed moderate-to-severe influenza A and/or B disease due to any seasonal influenza strain was demonstrated if the LL of the two-sided 95% CI of VE was >15%.
- The efficacy of Fluarix Tetra in protecting against any culture-confirmed influenza A and/or B disease due to any seasonal influenza strain was demonstrated if the LL of the two-sided 95% CI of VE was >10%.
- The efficacy of Fluarix Tetra in protecting against AOM associated with RT-PCR confirmed influenza A and/or B infection due to any seasonal influenza strain was demonstrated if the LL of the two-sided 95% CI of VE was >10%.
- The efficacy of Fluarix Tetra in protecting against RT-PCR confirmed severe influenza A and/or B disease due to any seasonal influenza strain was demonstrated if the LL of the two-sided 95% CI of VE was >15%.

Figure 2: Final analysis of efficacy objectives in D-QIV-004



Analysis of immunogenicity

The primary analysis was based on the ATP cohort for analysis of immunogenicity and was performed on the subjects from the immuno sub-cohort for each vaccine strain, overall (all cohorts pooled) and by cohort. Since the percentage of subjects excluded from the ATP cohort for analysis of immunogenicity was greater than 5%, a second analysis based on the TVC was performed to complement the ATP analysis, as per the statistical analysis plan.

Within groups assessment

For the humoral response in terms of HI antibodies for all vaccine strains, the following parameters were calculated by group for subjects from the immuno sub-cohort: GMT of HI at Day 0 and at Day 28/56 with 95% CI; SCR at Day 28/56 with 95% CI; MGI at Day 28/56 with 95% CI; SPR at Day 0 and at Day 28/56 with exact 95% CI. For the humoral response in terms of neutralising and anti-neuraminidase antibodies, the following parameters were calculated, by group, for a subset of subjects from the immuno sub-cohort: Seropositivity and GMTs at Days 0 and at Day 28/56 with 95% CI; Vaccine response rate (VRR) at Day 28/56 with 95% CI; MGI at Day 28/56 with 95% CI.

Analysis of safety

The primary analysis was performed on the TVC. The % of subjects with ≥ 1 local AE (solicited and unsolicited), with ≥ 1 general AE (solicited/unsolicited) and with any AE (solicited and unsolicited) during the 7 day follow-up period were tabulated with their exact 95% CIs after each vaccine dose and overall. The % of doses followed by ≥ 1 local AE (solicited/unsolicited), by at least one general AE (solicited/unsolicited) and by any AE (solicited/unsolicited) were tabulated in the same table. The same tabulation was done for subjects with ≥ 1 local solicited AE, with ≥ 1 general solicited AE and with any solicited AE during the 7 day solicited follow-up period. The same tabulation was also done for Grade 3 AEs, related AEs and Grade 3 related AEs. The % of subjects reporting each individual solicited local (any, Grade 3 and medically attended) and general (any, Grade 3, related, Grade 3 related and medically attended) AE during the 7 day solicited follow-up period were tabulated with exact 95% CI. The % of doses followed

by each individual solicited local and general AE were tabulated, with exact 95% CI. Occurrence of fever was reported per 0.5°C cumulative increments starting from 38°C by any route. The % of subjects with ≥1 report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 28 days after vaccination tabulated with exact 95% CI. The same tabulation was performed for Grade 3 unsolicited AEs, for unsolicited AEs with a relationship to vaccination and Grade 3 unsolicited AEs with relationship to vaccination. The % of subjects and % of doses reporting AEs resulting in a MAV were tabulated. AEs with MAVs, SAEs and pIMDs collected and summarised throughout the study duration.

6.2.1.12. Participant flow

Study population

TVC = 12,018 subjects (6,006 in the Fluarix Tetra group and 6,012 in the control group. Out of these, 11,205 subjects (5604 Fluarix Tetra and 5601 Control) were included in the ATP-E cohort, 11404 subjects (5707 Fluarix Tetra and 5697 Control) were included in the ATP-E - Time to event cohort, and 11,612 subjects (96.6%) (5,808 in the Fluarix Tetra group and 5,804 in the control group) completed the study. From the 1578 subject (933 Fluarix Tetra and 645 Control) enrolled in the immuno sub-cohort, 1332 subjects (753 Fluarix Tetra and 579 Control) were included in the ATP cohort for immunogenicity.

6.2.1.1. Major protocol violations/deviations

During the conduct of the study, the following important deviations from GCP compliance were identified by GSK for which an elimination code was attributed to a subject. It is possible that one subject received more than one elimination code.

Deviations related to ICF

21 subjects related to an invalid ICF.

Deviations related to concomitant vaccination not allowed by the protocol

1 subject received a vaccine during the study that was not allowed.

Deviations related to randomisation

10 subjects received a code for randomisation failure.

Deviations related to unblinding

224 subjects received a code for randomisation code broken.

Deviations related to vaccination not performed according to protocol

5 subjects received a vaccine not compatible with the vaccine regimen.

Deviations related to inclusion/exclusion criteria

15 subjects encountered a violation of inclusion/exclusion criteria.

Deviations related to administration of medication not allowed by the protocol

4 subjects received a medication not allowed by the study protocol.

Deviations related to non-compliance to the vaccination schedule

In 248 subjects, the second vaccine dose was provided outside the allowed interval.

Deviation related to blood samples

220 subjects did not comply with blood-sampling.

Deviations related to drop-outs

9 subjects dropped-out before the start of the surveillance period. This elimination code was only applicable for efficacy analyses.

Table 5: Summary of withdrawals, protocol violations and lost to follow-up in D-QIV-004

	D-QIV	Control	Total
Number of subjects vaccinated	6006	6012	12018
Number of subjects completed	5808	5804	11612
Number of subjects withdrawn	198	208	406
Reasons for withdrawal :			
Serious Adverse Event	1	6	7
Non-Serious Adverse Event	3	10	13
Protocol violation	1	0	1
Consent withdrawal (not due to an adverse event)	140	129	269
Migrated/moved from study area	20	23	43
Lost to follow-up (subjects with incomplete vaccination course)	6	16	22
Lost to follow-up (subjects with complete vaccination course)	17	19	36
Sponsor study termination	0	0	0
Others	10	5	15

D-QIV = Subjects who received the FLU D-QIV Vaccine

Control = Subjects who received the Control vaccine (Havrix/Varivax/Varinix/Prevnar)

Vaccinated = number of subjects who were vaccinated in the study

Completed = number of subjects who completed last study visit

Withdrawn = number of subjects who did not come back for the last visit

6.2.1.2. Baseline data

Mean age of the subjects in the TVC (Table 5) at vaccination dose 1 was 21.9 months in the Fluarix Tetra group and 21.8 months in the Control group, with an approx. equal distribution of males and females in both groups. Most subjects were of South East Asian (27.7% in both study groups), White - Caucasian /European (24.5% in the Fluarix Tetra group and 24.7% in the Control group) or other heritage (27.3% in both study groups). Of the 12018 subjects in the TVC, 11921 subjects (5958 Fluarix Tetra and 5963 Control) were un-primed at enrolment, and 97 subjects (48 Fluarix Tetra and 49 Control) were primed, per protocol definition. In Bangladesh, India, Honduras, Belgium, Czech Republic, Turkey, and the UK, only subjects that were ≥12 months of age were enrolled. In the TVC, the mean age of the subjects at vaccination dose 1 was 21.9 months in the Fluarix Tetra group and 21.8 months in the Control group, with an approx. equal distribution of males and females in both. Overall, most subjects were of Asian (27.7% Asian - South East Asian, 17.6% Asian Central/South Asian), White - Caucasian / European (24.6%) or other (mostly mixed race and Hispanic) heritage (27.3%). Baseline demographics of the ATP Cohort are shown in Table 6.

Table 6: Summary of demographic characteristics (Total vaccinated cohort) in D-QIV-004

Characteristics	Parameters or Categories	D-QIV N = 6006		Control N = 6012		Total N = 12018	
		Value or n	%	Value or n	%	Value or n	%
Age (months) at vaccination dose: 1	Mean	21.9	-	21.8	-	21.9	-
	SD	8.0	-	8.0	-	8.0	-
	Median	22.0	-	22.0	-	22.0	-
	Minimum	6	-	6	-	6	-
	Maximum	35	-	43	-	43	-
Gender	Female	2933	48.8	2925	48.7	5858	48.7
	Male	3073	51.2	3087	51.3	6160	51.3
Geographic Ancestry	African Heritage / African American	24	0.4	20	0.3	44	0.4
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian Heritage	1062	17.7	1053	17.5	2115	17.6
	Asian - East Asian Heritage	2	0.0	0	0.0	2	0.0
	Asian - Japanese Heritage	2	0.0	0	0.0	2	0.0
	Asian - South East Asian Heritage	1661	27.7	1666	27.7	3327	27.7
	Native Hawaiian or Other Pacific Islander	3	0.0	0	0.0	3	0.0
	White - Arabic / North African Heritage	142	2.4	149	2.5	291	2.4
	White - Caucasian / European Heritage	1471	24.5	1482	24.7	2953	24.6
	Other	1639	27.3	1642	27.3	3281	27.3

D-QIV = Subjects who received the FLU D-QIV Vaccine

Control = Subjects who received the Control vaccine (Havrix/Varivax/Varinix/Prevnar)

N = total number of subjects

n/% = number / percentage of subjects in a given category

Value = value of the considered parameter

SD = standard deviation

Table 7: Summary of demographic characteristics (ATP cohort) in D-QIV-004

Characteristic	Parameters or Categories	D-QIV N = 5604		Control N = 5601		Total N = 11205	
		Value or n	%	Value or n	%	Value or n	%
Age (months) at vaccination dose: 1	Mean	21.9	-	21.8	-	21.9	-
	SD	8.0	-	8.0	-	8.0	-
	Median	22.0	-	22.0	-	22.0	-
	Minimum	6	-	6	-	6	-
	Maximum	35	-	35	-	35	-
Gender	Female	2752	49.1	2726	48.7	5478	48.9
	Male	2852	50.9	2875	51.3	5727	51.1
Geographic Ancestry	African Heritage / African American	16	0.3	16	0.3	32	0.3
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian Heritage	1044	18.6	1034	18.5	2078	18.5
	Asian - East Asian Heritage	2	0.0	0	0.0	2	0.0
	Asian - Japanese Heritage	2	0.0	0	0.0	2	0.0
	Asian - South East Asian Heritage	1620	28.9	1611	28.8	3231	28.8
	Native Hawaiian or Other Pacific Islander	3	0.1	0	0.0	3	0.0
	White - Arabic / North African Heritage	129	2.3	138	2.5	267	2.4
	White - Caucasian / European Heritage	1241	22.1	1259	22.5	2500	22.3
	Other	1547	27.6	1543	27.5	3090	27.6

D-QIV = Subjects who received the FLU D-QIV Vaccine

Control = Subjects who received the Control vaccine (Havrix/Varivax/Varilrix/Prevnar)

N = total number of subjects

n/% = number / percentage of subjects in a given category

Value = value of the considered parameter

SD = standard deviation

6.2.1.3. Results for the primary efficacy outcome*Efficacy results*

Both primary confirmatory efficacy objectives were met. In the ATP-E - Time to event cohort, when compared to non-influenza vaccine controls in children 6 to 35 months:

- Fluarix Tetra was efficacious in preventing RT-PCR confirmed moderate-to-severe influenza A and/or B disease due to any seasonal strain; VE 63.2% (LL of 97.5% CI: 51.8%, that is, LL> 25% pre-specified success criterion) (Table 7).
- Fluarix Tetra was efficacious in preventing RT-PCR confirmed influenza A and/or B disease of any severity due to any seasonal strain; VE 49.8% (LL of 97.5% CI: 41.8%, that is, LL> 15% prespecified success criterion) (Table 8).

Table 8: Vaccine efficacy for RT-PCR confirmed moderate-to-severe influenza - confirmatory primary objective (ATP cohort for efficacy - Time to event) in D-QIV-004

Event Type	Group	AR						VE			
		N	n	%	97.5% CI		T(month)	T/N	%	97.5% CI	
					LL	UL				LL	UL
RT-PCR confirmed influenza - Moderate to severe	D-QIV	5707	90	1.58	1.23	1.99	24728.0	4.3	63.2	51.8	72.3
	Control	5697	242	4.25	3.67	4.89	24463.7	4.3	-	-	-

D-QIV = Subjects who received the Flu D-QIV Vaccine

Control = Subjects who received the Control vaccine (Havrix/Varivax/Varilrix/Prevnar)

N = number of subjects in each group

n = number of subjects reported at least one event in the reporting period

AR = attack rate = n/N (%) = percentage of subjects reported at least one event

T(month) = sum of follow-up periods expressed in months in each group

T/N = mean follow-up period in each group

VE (%) = Vaccine efficacy (Cox regression model adjusted for age category and stratified for cohort)

97.5%CI=97.5% exact confidence interval for AR, profile likelihood confidence interval for VE, LL=Lower Limit,

UL=Upper Limit

Table 9: Vaccine efficacy for RT-PCR confirmed influenza of any severity - confirmatory primary objective (ATP cohort for efficacy - Time to event) in D-QIV-004

Synopsis Table 3: Vaccine efficacy for RT-PCR confirmed influenza of any severity - confirmatory primary objective (ATP cohort for efficacy - Time to event)

Event Type	Group	N	n	%	AR		T(month)	T/N	%	VE	
					LL	UL				LL	UL
RT-PCR confirmed influenza - Any severity	D-QIV	5707	344	6.03	5.34	6.77	24076.4	4.2	49.8	41.8	56.8
	Control	5697	662	11.62	10.68	12.61	23343.7	4.1	-	-	-

D-QIV = Subjects who received the Flu D-QIV Vaccine
Control = Subjects who received the Control vaccine (Havrix/Varivax/Vanivax/Prevnar)
N = number of subjects in each group
n = number of subjects reported at least one event in the reporting period
AR = attack rate = n/N (%) = percentage of subjects reported at least one event
T(month) = sum of follow-up periods expressed in months in each group
T/N = mean follow-up period in each group
VE (%) = Vaccine efficacy (Cox regression model adjusted for age category and stratified for cohort) 97.5% CI = 97.5% exact confidence interval for AR, profile likelihood confidence interval for VE, LL=Lower Limit, UL=Upper Limit

6.2.1.4. Results for other efficacy outcomes

All secondary confirmatory efficacy objectives (evaluated sequentially) were met, except for the last secondary objective related to prevention of RT-PCR confirmed severe influenza disease, because the incidence of severe cases was too low for the analysis to be conclusive. In the ATP-E-Time to event, when compared to non-influenza vaccine controls in children 6 to 35 months:

- Fluarix Tetra was efficacious in the prevention of LRI associated with RT-PCR confirmed influenza A and/or B; VE: 54.0 % (LL of 95% CI: 28.9%, that is, >15% pre-specified success criterion).
- Fluarix Tetra was efficacious in the prevention of culture confirmed moderate-to-severe influenza A and/or B disease due to antigenically-matching influenza strains; VE: 77.6% (LL of 95% CI: 64.3 %, that is, >15% pre-specified success criterion).
- Fluarix Tetra was efficacious in the prevention of culture confirmed influenza A and/or B of any severity due to antigenically-matching influenza strains; VE: 60.1% (LL of the 95% CI: 49.1 %, that is, >15% pre-specified success criterion).
- Fluarix Tetra was efficacious in the prevention of culture confirmed moderate-to-severe influenza A and/or B disease due to any seasonal influenza strains; VE: 63.8% (LL of the 95% CI: 53.4%, that is, >15% pre-specified success criterion).
- Fluarix Tetra was efficacious in the prevention of culture confirmed influenza A and/or B disease of any severity due to any seasonal influenza strains; VE: 51.2% (LL of the 95% CI: 44.1 %, that is, >10% pre-specified success criterion).
- Fluarix Tetra was efficacious in the prevention of AOM associated with RT-PCR confirmed influenza A and/or B disease; VE: 56.6% (LL of the 95% CI: 16.7 %, that is, >10% prespecified success criterion).
- The analysis of Fluarix Tetra VE in the prevention of RT-PCR confirmed severe influenza A and/or B was inconclusive; VE: 34.2% (LL of the 95% CI: -297.3%, that is, <15% pre-specified success criterion).

Table 10: Vaccine efficacy for the seven secondary objectives - confirmatory secondary objectives (ATP cohort for efficacy - Time to event) in D-QIV-004

Event Type	Group	N	n	%	AR			VE			
					LL	UL	T(month)	T/N	%	LL	UL
RT-PCR confirmed influenza - LRI	D-QIV	5707	28	0.49	0.33	0.71	24890.5	4.4	54.0	28.9	71.0
	Control	5697	61	1.07	0.82	1.37	24898.1	4.4	-	-	-
Vaccine matching culture confirmed influenza - Moderate to severe	D-QIV	5707	20	0.35	0.21	0.54	24909.5	4.4	77.6	64.3	86.6
	Control	5697	88	1.54	1.24	1.90	24836.3	4.4	-	-	-
Vaccine matching culture confirmed influenza - Any severity	D-QIV	5707	88	1.54	1.24	1.90	24754.7	4.3	60.1	49.1	69.0
	Control	5697	216	3.79	3.31	4.32	24525.7	4.3	-	-	-
Culture confirmed influenza - Moderate to severe	D-QIV	5707	79	1.38	1.10	1.72	24756.1	4.3	63.8	53.4	72.2
	Control	5697	216	3.79	3.31	4.32	24528.3	4.3	-	-	-
Culture confirmed influenza - Any severity	D-QIV	5707	303	5.31	4.74	5.92	24177.1	4.2	51.2	44.1	57.6
	Control	5697	602	10.57	9.78	11.39	23517.6	4.1	-	-	-
RT-PCR confirmed influenza - AOM	D-QIV	5707	12	0.21	0.11	0.37	24930.6	4.4	56.6	16.7	78.8
	Control	5697	28	0.49	0.33	0.71	24977.4	4.4	-	-	-
RT-PCR confirmed influenza - Severe	D-QIV	5707	2	0.04	0.00	0.13	24956.2	4.4	34.2	-297.3	91.3
	Control	5697	3	0.05	0.01	0.15	25031.0	4.4	-	-	-

D-QIV = Subjects who received the Flu D-QIV Vaccine
Control = Subjects who received the Control vaccine (Havrix/Varivax/Varirix/Prevnar)
N = number of subjects in each group
n = number of subjects reported at least one event in the reporting period
AR = attack rate = n/N (%) = percentage of subjects reported at least one event
T(month) = sum of follow-up periods expressed in months in each group
T/N = mean follow-up period in each group
VE (%) = Vaccine efficacy (Cox regression model adjusted for age category and stratified for cohort)
95%CI=95% exact confidence interval for AR, profile likelihood confidence interval for VE, LL=Lower Limit, UL=Upper Limit. These secondary objectives were evaluated sequentially starting from event in first row to seventh row

Immunogenicity results

Fluarix Tetra elicited a robust post-vaccination (28 days) immune response against all four strains contained in the vaccine. In the ATP cohort for immunogenicity (all cohorts pooled) (see Tables 10 and 11 below):

- Pre-vaccination seropositivity rates were 26.9% (A/H1N1), 35.7% (A/H3N2), 27.5% (B/Victoria) and 18.0% (B/Yamagata) for Fluarix Tetra. Similar rates observed in the control group. Pre vaccination HI GMTs for Fluarix Tetra ranged from 7.3 to 11.9 across strains, and were very similar (7.3-13.4) for the control group.
- Post-vaccination seropositivity rates were 96.8% (A/H1N1), 98.3% (A/H3N2), 93.5% (B/Victoria) and 95.5% (B/Yamagata) for Fluarix Tetra, versus 29.4%, 36.3%, 25.4%, and 18.7%, respectively, for the control group.
- Post-vaccination SCRs were 80.2% (A/H1N1), 68.8% (A/H3N2), 69.3% (B/Victoria) and 81.2 (B/Yamagata) for Fluarix Tetra, versus 3.5%, 4.2%, 0.9%, and 2.3%, respectively, for the control group.
- Post-vaccination SPRs for Fluarix Tetra were 85.1% (A/H1N1), 81.3% (A/H3N2), 71.9% (B/Victoria) and 84.7% (B/Yamagata), versus 25.3%, 30.3%, 17.4%, and 11.1%, respectively, for the control group.
- Post-vaccination HI GMTs for the Fluarix Tetra group were 165.3 (A/H1N1), 132.1 (A/H3N2), 92.6 (B/Victoria) and 121.4 (B/Yamagata), versus 12.6, 14.7, 9.2, and 7.6, respectively, for control group.
- Post-vaccination MGIs for Fluarix Tetra were 14.0 (A/H1N1), 9.0 (A/H3N2), 9.3 (B/Victoria) and 16.7 (B/Yamagata), versus post-vaccination MGIs of 1.1, 1.1, 1.0, and 1.1, respectively, for the control group.

The post-vaccination immune responses in each of the 5 cohorts separately were comparable.

Health care utilisation and missed days off Day care/school and work for parents/LAR(s)

In the Fluarix Tetra group, the risk of visits to the GP or paediatrician were reduced by 46 % (RR 0.54 [0.47-0.62]) and to the ER by 79% (RR 0.21 [0.09-0.51]) for RT-PCR confirmed influenza cases of any severity. In the Tetra Fluarix group, the risk of GP or paediatrician visits and the risk of ER visits for RT-PCR confirmed moderate-to-severe influenza cases was reduced by 65% (RR 0.35[0.27-0.46]) and 80% (RR 0.20[0.06-0.69]) respectively, versus the control group. The use of Fluarix Tetra reduced the risk of missing a day from paid work for parent(s)/LAR(s) by

53% (RR 0.47 [0.28-0.79]) or Day care/school for the child by 57% (RR 0.43[0.30-0.62]) for RT-PCR confirmed influenza cases of any severity. The use of Fluarix Tetra reduced the risk of missing a day from paid work for parent(s)/LAR(s) by 65% (RR 0.35 [0.15-0.83]) or from Day care/school for the child by 54% (RR 0.46[0.27-0.77]) for RT-PCR confirmed moderate-to-severe influenza cases

Use of adjunctive agents and/or antibiotics

In the Fluarix Tetra group versus control group, there was less use of antipyretics (5.8% versus 10.8%) and antibiotics (3% vs 5.9%) for RT-PCR confirmed influenza cases of any severity, as well as for RT-PCR confirmed moderate to severe influenza (1.4% versus 3.9% and 0.8% versus 2.6%, respectively).

Table 11: Summary of HI antibody parameters (Seropositivity rates, SPR) at pre and post vaccination (ATP cohort for immunogenicity) in D-QIV-004

Antibody	Group	Timing	N		≥10 1/DIL			SPR			
			n	%	LL	UL	n	%	LL	UL	
Flu A (H1N1) HI	D-QIV	PRE	744	200	26.9	23.7	30.2	182	24.5	21.4	27.7
		POST	752	728	96.8	95.3	97.9	640	85.1	82.4	87.6
	Control	PRE	567	152	26.8	23.2	30.7	134	23.6	20.2	27.4
		POST	578	170	29.4	25.7	33.3	146	25.3	21.8	29.0
Flu A (H3N2) HI	D-QIV	PRE	746	266	35.7	32.2	39.2	238	31.9	28.6	35.4
		POST	753	740	98.3	97.1	99.1	612	81.3	78.3	84.0
	Control	PRE	568	187	32.9	29.1	37.0	159	28.0	24.3	31.9
		POST	578	210	36.3	32.4	40.4	175	30.3	26.6	34.2
Flu B (Victoria) HI	D-QIV	PRE	745	205	27.5	24.3	30.9	143	19.2	16.4	22.2
		POST	750	701	93.5	91.5	95.1	539	71.9	68.5	75.1
	Control	PRE	567	138	24.3	20.9	28.1	103	18.2	15.1	21.6
		POST	579	147	25.4	21.9	29.1	101	17.4	14.4	20.8
Flu B (Yamagata) HI	D-QIV	PRE	745	134	18.0	15.3	20.9	73	9.8	7.8	12.2
		POST	753	719	95.5	93.7	96.9	638	84.7	82.0	87.2
	Control	PRE	568	93	16.4	13.4	19.7	59	10.4	8.0	13.2
		POST	579	108	18.7	15.6	22.1	64	11.1	8.6	13.9

D-QIV = Subjects who received the Flu D-QIV Vaccine
Control = Subjects who received the Control vaccine (Havrix/Varivax/Varirix/Prevnar)
Seroprotection rate (SPR) = Subjects with antibody titres ≥40 1/DIL
N = Number of subjects with results available (for seropositivity rates and SPR computation)
n/% = number/percentage of subjects with titre equal to or above specified value
n/% = Number/percentage of seroprotected subjects
95% CI = 95% confidence interval: LL = Lower Limit UL = Upper Limit
PRE = Pre-vaccination at Day 0
POST = Post-vaccination 1 at Day 28 for primed subjects or post-vaccination 2 at Day 56 for unprimed subjects

Table 12: Summary of HI antibody parameters (GMT, SCR and MGI) at pre and post vaccination (ATP cohort for immunogenicity) in D-QIV-004

Antibody	Group	Timing	N		GMT			SCR			MGI			
			n	%	Value	LL	UL	n	%	LL	UL	Value	LL	UL
Flu A (H1N1) HI	D-QIV	PRE	744	11.9	10.6	13.2	-	-	-	-	-	-	-	-
		POST	752	165.3	148.6	183.8	743	596	80.2	77.2	83.0	14.0	12.8	15.3
	Control	PRE	567	11.9	10.5	13.5	-	-	-	-	-	-	-	-
		POST	578	12.8	11.1	14.3	566	20	3.5	2.2	5.4	1.1	1.0	1.1
Flu A (H3N2) HI	D-QIV	PRE	746	14.9	13.2	16.5	-	-	-	-	-	-	-	-
		POST	753	132.1	119.1	146.5	746	513	68.8	65.3	72.1	9.0	8.2	9.8
	Control	PRE	568	13.4	11.8	15.2	-	-	-	-	-	-	-	-
		POST	578	14.7	12.9	16.7	567	24	4.2	2.7	6.2	1.1	1.0	1.2
Flu B (Victoria) HI	D-QIV	PRE	745	10.0	9.1	11.0	-	-	-	-	-	-	-	-
		POST	750	92.6	82.3	104.1	742	514	69.3	65.8	72.6	9.3	8.6	10.2
	Control	PRE	567	9.2	8.3	10.1	-	-	-	-	-	-	-	-
		POST	579	9.2	8.4	10.1	567	5	0.9	0.3	2.0	1.0	1.0	1.1
Flu B (Yamagata) HI	D-QIV	PRE	745	7.3	6.8	7.8	-	-	-	-	-	-	-	-
		POST	753	121.4	110.1	133.8	745	605	81.2	78.2	84.0	16.7	15.2	18.3
	Control	PRE	568	7.3	6.8	7.9	-	-	-	-	-	-	-	-
		POST	579	7.6	7.0	8.3	568	13	2.3	1.2	3.9	1.1	1.0	1.1

D-QIV = Subjects who received the Flu D-QIV Vaccine
Control = Subjects who received the Control vaccine (Havrix/Varivax/Varirix/Prevnar)
Seroprotection rate (SCR) defined as:
For initially seronegative subjects, antibody titre ≥ 40 1/DIL at post-vaccination
For initially seropositive subjects, antibody titre at post-vaccination ≥ 4 fold the pre-vaccination antibody titre
GMT=geometric mean antibody titre calculated on all subjects
MGI=geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titre to the Day 0 reciprocal HI titre
N = Number of subjects with results available (for GMT computation)
n/% = Number of subjects with both pre and post results available (for SCR and MGI computation)
n/% = number/percentage of subjects with titre equal to or above specified value
n/% = Number/percentage of seroprotected subjects
n/% = Number/percentage of seroconverted subjects
95% CI = 95% confidence interval: LL = Lower Limit UL = Upper Limit
PRE = Pre-vaccination at Day 0
POST = Post-vaccination 1 at Day 28 for primed subjects or post-vaccination 2 at Day 56 for unprimed subjects

Safety

This is presented in detail in Section 7.0. No safety signals of concern were revealed.

6.2.1.5. Evaluator commentary

Fluarix Tetra was efficacious in preventing both RT-PCR confirmed moderate-to-severe influenza A and/or B disease due to any seasonal strain and any severity influenza when

compared to non-influenza vaccine controls in children 6 to 35 months. Thus the primary objectives of the study were achieved. All secondary confirmatory efficacy objectives (evaluated sequentially) were met, except for the last objective related to prevention of RT-PCR confirmed severe influenza disease, because there were too few cases. Fluarix Tetra was immunogenic against all four vaccine strains, overall (pooled results of 5 cohorts) and in each cohort, as assessed by HI antibody titres. Fluarix Tetra was generally well tolerated and no safety concern was identified.

6.3. Other efficacy studies

6.3.1. Studies D-QIV-009 EXT 004 (116023) and D-QIV-015 (201251) (6 to 35 months cohort)

6.3.1.1. D-QIV-009 EXT 004 (116023)

Immunogenicity, safety and reactogenicity study of Fluarix Tetra, administered to children who previously participated in D-QIV-004 (see above, pivotal study).

Study Date

Study initiation date: 06 October 2012; Study completion date: 05 June 2013.

Data lock point (Date of database freeze)

23 Aug 2013 and 11 Dec 2013 for neutralising antibody and anti-neuraminidase antibody analyses, 27-Sep-2016 for immunogenicity analysis excluding subjects who had an RT-PCR confirmed influenza infection in D-QIV-004.

Design

See Figure 1.

Study objectives: Primary

To assess HI antibody titre at Day 7 after one dose of Fluarix Tetra (2012-2013 formulation) in vaccine primed and vaccine un-primed subjects, for all strains included in the vaccine.

Secondary

1) To assess the GMT ratio of vaccine primed to vaccine-un-primed subjects, for all strains included in the vaccine at Day 7 after one dose of Fluarix Tetra (2012-2013 formulation); 2) To assess the difference in SCR between vaccine primed and vaccine-un-primed subjects, for all strains included in the vaccine at Day 7 after one dose of Fluarix Tetra (2012-2013 formulation); 3) To assess the difference in SPR between vaccine primed and vaccine-un-primed subjects, for all strains included in the vaccine at Day 7 after one dose of Fluarix Tetra (2012-2013 formulation); 4) To categorize the risk profile by assessing the % of subjects with HI antibody titres <1:10, 1:10 to <1:40, and \geq 1:40 at Day 0 and at Day 7 after one dose of Tetra Fluarix (2012-2013 formulation); 5) To assess neutralising & anti-neuraminidase antibody responses (subset of 226); 6) To assess immune response by age gp; 7) To assess safety of the study vaccine during the entire study period and the reactogenicity of the study vaccine after the first dose

6.3.1.2. Study vaccines

1x IM dose of Tetra Fluarix at Visit 1 (Day 0) for vaccine primed subjects; 2 doses IM: at Visit 1 (Day 0) and Visit 3 (Day 28) for vaccine un-primed subjects (Table 12).

6.3.1.3. Study population

Healthy male or female children between and including 17 to 48 months of age at the time of the first vaccination who received a 2 dose vaccination in D-QIV-004 (Table 13).

Table 13: Overview of strains included in the influenza vaccines in D-QIV-009, D-QIV-015

D-QIV-009	
Countries	Czech Republic, Poland, Spain, UK
Vaccination season	2012-2013
Flu A (H1N1) HI	A/Christchurch/16/2010 (NIB-74xp) †
Flu A (H3N2) HI	A/Victoria/361/2011 (IVR-165) †
Flu B (Victoria) HI	B/Brisbane/60/2008 (Victoria) †
Flu B (Yamagata) HI	B/Hubei-Wujiagang/158/2009 (NYMC BX-39) †
D-QIV-015	
Countries*	Bangladesh, France, Germany, Spain, Poland
Vaccination season	2014-2015
Flu A (H1N1) HI	A/Christchurch/16/2010 ††
Flu A (H3N2) HI	A/Texas/50/2012 ††
Flu B (Victoria) HI	B/Brisbane/60/2008 ††
Flu B (Yamagata) HI	B/Massachusetts/02/2012 ††

* Countries enrolling subjects in the 6-35 month cohort

† Recommended WHO composition for 2012-2013 season quadrivalent vaccine

†† Recommended WHO composition for Northern Hemisphere 2014-2015 season quadrivalent vaccine

Table 14: Study Population in D-QIV-009

Number of subjects	Vaccine-primed Group	Vaccine-unprimed Group
Planned, N	226	226
Enrolled, N (Total Vaccinated Cohort)	241	229
Completed, n (%)	238 (98.8)	221 (96.5)
Demographics (Total Vaccinated cohort):		
Females:Males	114:127	96:133
Mean Age, months (SD)	33.2 (7.54)	32.5 (7.39)
White - Caucasian / European heritage, n (%)	236 (97.9)	224 (97.8)
Vaccine-primed group received 2 doses of Flu D-QIV in Study 115345 and received 1 dose of Flu D-QIV in this study Vaccine-unprimed group received 2 doses of a non-Flu vaccine in Study 115345 and received 2 doses of Flu D-QIV in this study		
N = total number of subjects; n/% = number/percentage of subjects; SD = standard deviation		

6.3.1.4. Immunogenicity primary analysis

The primary analysis was based on the according-to-protocol (ATP) cohort for analysis of immunogenicity (ATP-I). A complementary analysis based on the TVC was also performed since there were >5% of the subjects excluded from the ATP-I.

6.3.1.5. Immunogenicity results

In the ATP-I, the vaccine primed group, SCRs ranged between 76.5% - 94.1% across the 4 vaccine strains and the highest SPR observed was 96.9% (for A/Christchurch/16/2010 (H1N1) and B/Brisbane/60/2008 (Victoria)), 7 days after the revaccination dose. In the vaccine unprimed group, SCRs ranged between 32.2% and 38.6% across the 4 vaccine-strains and the highest SPR observed was 40.2% for B/Brisbane/60/2008 (Victoria), 7 days after the first dose of Tetra Fluarix. Similar results were obtained for vaccine primed and un-primed subjects, respectively, in the ATP-I excluding subjects who had an RTPCR confirmed influenza infection in Study D-QIV-004. Compared to the vaccine un-primed group, 7 days post-vaccination, SCRs were 37.9% to 56.0% higher and the SPRs were 47.4% to 62.4% higher in the vaccine primed group, across the 4 strains, for the ATP-I. The distribution of subjects with HI titres $\geq 1:80$ (highest titre category assessed) at Day 7 post-Dose 1 ranged from 70.5% to 96.0% among primed subjects and from 24.4% to 37.8% among un-primed subjects, for the ATP-I. Similar patterns for SCRs, SPRs, and distribution of HI titres were observed for the ATP-I excluding subjects who had an RT-PCR confirmed influenza infection in D-QIV-004. The B/Victoria strain was identical between the Fluarix Tetra used in the primary vaccination (D-QIV-004, cohort 1) and Fluarix Tetra used in the revaccination (Study D-QIV-009), and although the A/H1N1 strains were not identical, they were antigenically similar. In the ATP-I, a heterologous revaccination response was observed with a SCR of 81.4% and 94.1% and a SPR of 86.2% and 96.4% for the A/Victoria/361/2011 (H3N2) and the B/Hubei-Wujiagang/158/2009 (Yamagata) strains respectively, which were different between the two vaccines, suggesting cross-priming for unmatched strains. A similar heterologous revaccination response was observed in the ATP-I excluding subjects who had an RT-PCR confirmed influenza infection in Study D-QIV-004. The

anamnestic response to a revaccination dose of Fluarix Tetra in vaccine primed subjects was further evaluated by an assessment of pre-revaccination (Day 0) and post re-vaccination (Day 7) GMTs. For the ATP-I, the GMT for HI antibodies titres at Day 0 ranged between 11.9 and 43.1 in the vaccine primed group, in contrast to between 6.5 and 16.4 in the vaccine un-primed group, while the GMTs at Day 7 ranged between 135.3 and 445.6 in the vaccine primed group, and between 26.1 and 47.5 in the vaccine-un-primed group. The HI adjusted GMT ratios of vaccine primed/vaccine un-primed subjects 7 days after the first dose of Fluarix Tetra, ranged from 2.70 to 8.97 across the 4 vaccine strains. Similar results, in terms of GMTs and adjusted GMT ratios, were obtained for the ATP-I excluding subjects who had an RT-PCR confirmed influenza infection in D-QIV-004. This early anamnestic revaccination response seen for the 4 vaccine strains in the vaccine primed group was observed in both age sub-strata. HI antibody persistence a year after the priming dose was evaluated by assessing pre-revaccination (Day 0) GMTs. For the ATP-I, the GMTs at Day 0 ranged between 11.9 and 43.1 in the vaccine primed group, in contrast to between 6.5 and 16.4 in the vaccine un-primed group. For the two strains similar for priming (A/H1N1 and B/Victoria), pre-revaccination GMTs at Day 0 were higher in the group primed with Fluarix Tetra compared to the un-primed group showing that the immune response persisted one year after priming. Although the HI antibodies were not tested against the priming strains, HI titre was also higher against B/Yamagata, but not against A/H3N2 strain in the D-QIV-009 vaccine primed group versus un-primed group. A similar pattern as described above was seen, for neutralising and anti-neuraminidase antibody immune response, for both ATP-I cohorts.

Table 15: Summary of immunogenicity results at Day 0 (Pre) and Day 7 post-Dose 1: seropositivity rates (HI antibody titres $\geq 1:10$), GMTs and seroprotection rates (SPRs) (ATP-I) in D-QIV-009

Group	Time	N	$\geq 1:10$			GMT			SPR ($\geq 1:40$)					
			n	%	95% CI		Value	95% CI		N	n	%	95% CI	
					LL	UL		LL	UL				LL	UL
A/Christchurch/16/2010 (H1N1)														
Vaccine-primed	PRE	221	189	85.5	80.2	89.9	43.1	33.8	54.9	221	89	40.3	33.7	47.1
	P1D7	224	220	98.2	95.5	99.5	445.6	376.9	526.7	224	217	96.9	93.7	98.7
Vaccine-unprimed	PRE	202	64	31.7	23.3	38.6	14.5	11.5	18.2	202	61	30.2	24.0	37.0
	P1D7	209	137	65.6	58.7	72.0	43.8	32.0	65.5	209	72	34.4	28.0	41.3
A/Victoria/361/2011 (H3N2)														
Vaccine-primed	PRE	221	131	59.3	52.5	65.8	12.3	10.7	14.1	221	37	16.7	12.1	22.3
	P1D7	224	218	97.3	94.3	99.0	135.3	113.6	161.2	224	193	86.2	80.9	90.4
Vaccine-unprimed	PRE	202	79	39.1	32.3	46.2	16.4	13.2	20.4	202	74	36.6	30.0	43.7
	P1D7	209	99	47.4	40.4	54.4	47.5	32.6	69.3	209	81	38.8	32.1	45.7
B/Brisbane/60/2008 (Victoria)														
Vaccine-primed	PRE	221	187	84.6	79.2	89.1	28.5	23.8	34.1	221	72	32.6	26.4	39.2
	P1D7	224	224	100	98.4	100	193.9	168.7	222.8	224	217	96.9	93.7	98.7
Vaccine-unprimed	PRE	202	58	28.7	22.6	35.5	10.0	8.4	11.9	202	39	19.3	14.1	25.4
	P1D7	209	174	83.3	77.5	88.0	47.1	35.2	63.0	209	84	40.2	33.5	47.2
B/Hubei-Wujiagang/158/2009 (Yamagata)														
Vaccine-primed	PRE	221	134	60.6	53.9	67.1	11.9	10.6	13.3	221	27	12.2	8.2	17.3
	P1D7	224	222	99.1	96.8	99.9	182.6	159.0	209.6	224	216	96.4	93.1	98.4
Vaccine-unprimed	PRE	202	36	17.8	12.8	23.8	6.5	5.9	7.2	202	12	5.9	3.1	10.1
	P1D7	209	144	68.9	62.1	75.1	26.1	20.9	32.7	209	83	39.7	33.0	46.7

Vaccine-primed= vaccine-primed group received 2 doses of Flu D-QIV in Study 115345 and received 1 dose of Flu D-QIV in this study
Vaccine-unprimed= vaccine-unprimed group received 2 doses of a non-Flu vaccine in Study 115345 and received 2 doses of Flu D-QIV in this study
PRE = Pre-vaccination at Day 0
P1D7 = Post-vaccination Dose 1 at Day 7
SPR = percentage of subjects with a serum HI titre $\geq 1:40$
GMT = geometric mean HI antibody titre calculated on all subjects
SPR = Seroprotection rate
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

6.3.1.6. Safety results

See Section 7.0.

6.3.2. D-QIV-015 (6 to 35 months cohort only)

A Phase III, double-blind, randomized, multicentre study to assess safety and immunogenicity of GlaxoSmithKline Biologicals' Quadrivalent Split Virion Influenza Vaccine (GSK2321138A), Fluarix Tetra, manufactured with a new process, in adults aged 18 to 49 years and in children aged 6 months to 17 years. This study is currently in review by the TGA for another submission.

6.3.2.1. Study dates

Study initiation date: 18-Aug-2014; Study completion date: 18-Apr-2015

6.3.2.2. Data lock point (Date of database freeze)

16-Jul-2015

6.3.2.3. Design

The study was conducted as a Phase III, randomized, double-blind, controlled, multi-country study with staggered enrolment of adult and paediatric treatment groups. The subjects were randomized 1:1 to receive either Fluarix Tetra vaccine produced by the Investigational Process (IP) or Fluarix Tetra vaccine produced by the Licensed Process (LP).

6.3.2.4. Study vaccines

See Table 12.

6.3.2.5. Study population

See Table 15.

6.3.2.6. Immunogenicity and safety findings*Rationale for these post hoc analyses*

D-QIV-004 excluded children at risk of influenza complications as seasonal influenza vaccination is recommended. This exclusion criterion was not applied in D-QIV-015, and hence the findings allowed assessment of the impact of risk factors for influenza complications on vaccine immunogenicity. Furthermore, in both studies, the Bangladesh study centre recruited a substantial number of children 6 to 35 months of age with enrolment in D-QIV-015 and Cohort 5 of D-QIV-004 during the same influenza season. Therefore, the post hoc analysis of immunogenicity in 6 to 35 months old children from Bangladesh presented in this Annex Report 1 allows a contrast of Fluarix Tetra immunogenicity (from the Fluarix Tetra from investigational process (IP) group in D-QIV-015) to immunogenicity observed in the efficacy trial (Fluarix Tetra from the currently licensed process (LP)). In addition to the pre-specified, confirmatory non-inferiority analysis of the two processes in Study D-QIV-015, this post-hoc analysis provides additional support to bridge the immunogenicity of the two processes across studies. Lastly, an evaluation of safety by country was performed. Note: different procedure for collecting information on AEs (trained field workers, was used in Bangladesh).

Table 16: Study population subjects aged 6 to 35 months (Paediatric-TVC) in D-QIV-015

Number of subjects	D-QIV IP 6-35 m	D-QIV LP 6-35 m	Total
Planned, N	470	470	940
Randomised, N (Total Vaccinated Cohort)	466	474	940
Primed subjects completed, n (%)	40 (8.6)	41 (8.6)	81 (8.6)
Unprimed subjects completed, n (%)	419 (89.9)	420 (88.6)	839 (89.3)
Demographics			
	D-QIV IP 6-35 m	D-QIV LP 6-35 m	Total
N (Total Vaccinated Cohort)	466	474	940
Females:Males	223:243	209:265	432:508
Mean Age, months (SD)	19.7 (8.0)	19.9 (8.3)	19.8 (8.1)
Median Age, months (minimum, maximum)	19 (4, 36)*	19 (5, 35)*	19 (4, 36)*
White - Caucasian / European Heritage, n (%)	329 (70.6)	337 (71.1)	666 (70.9)
Asian - South East Asian Heritage, n (%)	91 (19.5)	91 (19.2)	182 (19.4)
White - Arabic / North African Heritage, n (%)	28 (6.0)	23 (4.9)	51 (5.4)
D-QIV IP = GSK Biologicals' quadrivalent influenza vaccine produced using the investigational process			
D-QIV LP = GSK Biologicals' quadrivalent influenza vaccine produced using the licensed process			
D-QIV IP 6-35 m = D-QIV IP (6-<36 months)			
D-QIV LP 6-35 m = D-QIV LP (6-<36 months)			
N = Total number of subjects			
n%= number/percentage of subjects			
SD = standard deviation			
the subject n°248, the Date of Birth = 2014 (with missing day and month). In this case, the 30th of June is applied for Date of Birth so the calculated age for this subject is 4 months.			
the subject n°112, the Date of Birth = APR2014 (with missing day). In this case, the 15th is applied for Date of Birth so the calculated age for this subject is 5 months.			
the subjects n°2205 & 2469, the Date of Birth = MAY2014 (with missing day). In this case, the 15th is applied for Date of Birth so the calculated age for these subjects is 5 months.			
* For the subject n°301, the Date of Birth = OCT2011 (with missing day). In this case, the 15th is applied so the calculated age for this subject is 36 months.			

6.3.2.7. Immunogenicity results by risk factor for influenza complications in children 6 to 35 months of age

In the Tetra Fluarix IP group, the HI GMTs across the 4 strains ranged from 40.5 to 191.9 among children with risk factor for influenza complications and from 30.2 to 91.8 among children without risk factor for influenza complications, 28 days post-vaccination. In the Tetra Fluarix LP group, the HI GMTs across the 4 strains ranged from 40.6 to 176.7 and from 37.2 to 102.2 among children with risk factor for influenza complications and without risk factor, respectively, 28 days postvaccination.

The Tetra Fluarix IP group with risk factor for influenza complications had an SCR of $\geq 58.2\%$ and a SPR of $\geq 59.3\%$ and the Tetra Fluarix IP group without risk factor had a SCR of $\geq 46.8\%$ and a SPR of $\geq 46.9\%$ for each vaccine strain. The Tetra Fluarix LP group with risk factor for influenza complications had a SCR of $\geq 51.5\%$ and a SPR of $\geq 52.5\%$ and the Tetra Fluarix LP group without risk factor had a SCR of $\geq 49.4\%$ and a SPR of $\geq 50.3\%$ for each vaccine strain. In the Tetra Fluarix IP group, the MGI ranged from 6.7 to 15.5 and from 5.3 to 11.4 for the strains among children with risk factor for influenza complications and children without, respectively. In the Tetra Fluarix LP group, the MGI ranged from 7.2 to 14.7 and from 6.4 to 12.9 for the strains among children with risk factor for influenza complications and children without risk factor, respectively.

Overall, the immune responses of children with risk factors for influenza complications and of those not at risk were comparable with respect to all 4 strains contained in the study vaccines, except for the A/H1N1 strain GMT values, which were *higher* in the at risk children. SCR for the A/H1N1 strain was similar in children with and without risk factors for influenza complications.

6.3.2.8. Immunogenicity results in children 6 to 35 months of age from Bangladesh

Twenty eight days post-vaccination, the HI GMTs across the 4 strains ranged from 36.7 to 104.7 in the Tetra Fluarix IP group, and from 48.2 to 107.4 in the Tetra Fluarix LP group. The Tetra Fluarix IP group had a SCR of $\geq 50.0\%$ and a SPR of $\geq 50.0\%$, and the Tetra Fluarix LP group had a SCR of $\geq 52.9\%$ and a SPR of $\geq 52.9\%$ for each vaccine strain. The MGI ranged from 5.7 to 10.2 for the strains in the Tetra Fluarix IP group and from 7.2 to 11.1 in the Tetra Fluarix LP group. When compared to the overall immunogenicity analysis including the entire study population 6 to 35 months of age, the immune response of children enrolled at the Bangladesh study centre was similar, except for the GMT values and baseline SPR for the A/H1N1 strain, which were lower for Bangladesh. SCR for the A/H1N1 strain was similar in children enrolled at the Bangladesh study centre and children enrolled across all countries.

Table 17: Adjusted GMT ratios of Flu A/H1N1, Flu A/H3N2, Flu B/Yamagata, Flu B/Victoria HI antibodies between groups (Fluarix Tetra LP/Fluarix Tetra IP) 28 days post last vaccination in subjects aged 6 to 35 months (Paediatric - ATP cohort for immunogenicity) in D-QIV-015

Antibody	D-QIV LP 6-35 m		D-QIV IP 6-35 m		Adjusted GMT ratio (D-QIV LP 6-35 m / D-QIV IP 6-35 m)		
	N	Adjusted GMT	N	Adjusted GMT	Value	95% CI	LL
Flu A/H1N1	424	105.3	431	98.0	1.07	0.90	1.28
Flu A/H3N2	423	56.3	431	47.7	1.18	1.00	1.39
Flu B/Yamagata	423	106.4	431	99.2	1.07	0.91	1.27
Flu B/Victoria	423	37.7	431	32.2	1.17	0.99	1.38

D-QIV IP = GSK Biologicals' quadrivalent influenza vaccine produced using the investigational process
D-QIV LP = GSK Biologicals' quadrivalent influenza vaccine produced using the licensed process
D-QIV IP 6-35 m = D-QIV IP (6-<36 months)
D-QIV LP 6-35 m = D-QIV LP (6-<36 months)
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for baseline titer - pooled variance); LL = lower limit, UL = upper limit

6.3.2.9. Safety result

See Section 7.0.

6.3.3. Evaluator commentary on other efficacy studies

6.3.3.1. D-QIV-009

The protocol-specified analysis of immunogenicity parameters (using the ATP-I excluding subjects who had an RT-PCR confirmed influenza infection in D-QIV-004) yielded results which were very similar to those of the ATP-I analysis inclusive of all eligible subjects. Therefore, study conclusions apply to both ATP-I analyses. The early and robust revaccination response (in terms of seropositivity, SPR, SCR, GMT, GMI, measured 7 days after revaccination) demonstrated that 2 primary doses of Tetra Fluarix in Tetra Fluarix-004, established immune memory in children 6 to 35 months of age that could be recalled in vaccine primed subjects, but not in the vaccine-un-primed subjects. The anamnestic response observed for the A/H1N1 and B/Victoria strains that were present in both the primary and subsequent year vaccines, as well as for the A/H3N2 and B/Yamagata strains that changed in the subsequent year vaccine, suggesting cross-priming for these unmatched strains. The vaccine primed subjects had higher SCRs and SPRs for all 4 vaccine strains compared to the vaccine-un-primed subjects.

There was also a heterologous response with respect to the 2 strains (A/H3N2 and B/Yamagata) that did not match between the Tetra Fluarix used for priming and revaccination. GMTs were also higher in vaccine primed subjects at 7 days post-vaccination compared to vaccine-un-primed subjects, as were adjusted GMT ratios. The anamnestic response was observed in both age sub-strata (17-29 and 30-48 months). The HI antibody response elicited by a 2-dose priming schedule in the parent study persisted up to a year as evidenced by higher Day 0 (pre-revaccination) GMTs for the 2 priming strains common with the revaccination strains (A/H1N1 and B/Victoria) in the vaccine primed group compared to the vaccine-un-primed group. The revaccination dose of Tetra Fluarix in the vaccine primed group and first Fluarix Tetra dose in the vaccine-un-primed group were well tolerated. No safety concerns were identified. See Section 7.0.

6.3.3.2. D-QIV-015

The immune responses of children with risk factors for influenza complications and those not at risk were comparable with respect to all 4 strains contained in Tetra Fluarix IP and Tetra Fluarix LP, except for the GMT values for the A/H1N1 strain, which were higher in the at risk children. When compared to the overall immunogenicity analysis including the entire study population 6 to 35 months of age, the immune response of children enrolled at the Bangladesh study centre was similar, except for the GMT values for the A/H1N1 strain, were lower for Bangladesh. Overall, Fluarix Tetra was generally well tolerated and no safety concern was identified. See Section 7.0.

6.4. Analyses performed across trials: pooled and meta analyses

The protective efficacy of Fluarix Tetra was demonstrated from data pooled from 5 independent cohorts in the D-QIV-004 study, enrolled over 5 influenza seasons, inclusive of seasons with mismatch between vaccine strains and circulating strains. See Section 6.2.

6.5. Evaluator's conclusions on clinical efficacy

6.5.1. Clinical vaccine efficacy

VE was shown in each age stratum. In the 6-17 months and 18-35 months age strata, with VE of 48.8% (95% CI: 21.2-67.4) and 68.5% (95% CI: 58.2-76.5), respectively for the prevention of RT-PCR confirmed moderate-to-severe influenza and 43.3% (95% CI: 27.8-55.8) and 51.6%

(95% CI: 43.7-58.4), respectively for the prevention of RT-PCR confirmed influenza of any severity. Although the 95% CI of VE by age group overlapped for the primary objectives and for the majority of the secondary objectives, the VE of Fluarix Tetra tended to be higher in the older age stratum (18-35 months of age) compared to the 6-17 months and the 6-11 months of age stratum.

6.5.1.1. Waning of vaccine efficacy over time

VE over the season was evaluated using a piecewise Cox model. There was no notable decrease in VE over time.

6.5.1.2. Immunogenicity

The HI immune response induced with Fluarix Tetra was evaluated in the three studies (in a sub-cohort in Study D-QIV-004).

HI immune response 28 days after vaccination (Studies D-QIV-004/-015)

The immune response (HI antibody titre) 28 days after vaccination (seropositivity rates, SPR, GMT, SCR, MGI) show that Fluarix Tetra was immunogenic against the four vaccine strains in both studies when given as one dose or two doses depending on the influenza vaccine priming status. For Study D-QIV-004, overall, there was a higher immune response in the 18-35 month age stratum (SPR from 79.8% to 92.5%, TVC) compared to the 6-17 month age stratum (SPR from 54.9% to 72.5%, TVC). Children in the 6-11 month age sub-stratum had lower immune responses (SPR from 38.2% to 55.3%, TVC) compared to the older children. Study D-QIV-015 demonstrated that immune responses were comparable in children with/without risks of influenza complications.

6.5.2. Persistence (at one year) and immunogenicity of a revaccination dose

For the two strains similar for priming and revaccination (A/H1N1 and B/Victoria), the Day 0 HI titres in Study D-QIV-009 were higher in subjects primed with Fluarix Tetra compared to unprimed subjects showing that the immune response persists one year after priming. The anamnestic (recall) response was observed against the four vaccine strains despite the fact that Fluarix Tetra composition was updated by strain changes from the priming to the revaccination year for H3N2 and B/Yamagata vaccine components, suggesting cross-priming between unmatched strains. The immunogenic non-inferiority of Tetra Fluarix IP to Tetra Fluarix LP in Study DQIV-015, 28 days after last vaccination support the efficacy of Fluarix Tetra manufactured with the new harmonised process. Importantly, in D-QIV-004, vaccination with Fluarix Tetra led to a reduction in healthcare utilisation (for example, visits to GP or paediatrician and emergency room visits), reduced time of nursery/school and lost workdays for parents/LAR(s). In addition, although antibiotic use was low, this was nearly halved in those receiving Fluarix Tetra.

7. Clinical safety

7.1. Methodology for safety assessment

- Solicited local symptoms (pain, redness and swelling at injection site) and solicited general symptoms (drowsiness, fever, irritability/fussiness and loss of appetite) within 7 days (Day 0-Day 6) after each vaccination in Studies D-QIV-004 and DQIV- 015, and after the first vaccination in Study D-QIV-009. In Study D-QIV-015, following request from a regulatory agency (CBER), oculorespiratory syndrome (ORS) was added as an additional secondary safety objective and was solicited within 3 days after vaccination (Day 0 - Day 2).

- Unsolicited AEs within 28 days (Day 0 - Day 27) after each vaccination in Studies DQIV-004 and D-QIV-015, and after the first vaccination in Study D-QIV-009.
- MAV and SAEs during the entire study period.
- pIMDs in Studies D-QIV-004 and D-QIV-009, during the entire study period.
- Adverse event of specific interest (anaphylaxis, febrile seizure, Bell's palsy, narcolepsy, injection site haemorrhage in individuals with thrombocytopenia or any other coagulation disorder, Guillain-Barré Syndrome) in Study D-QIV-015 during the entire study period (to be reported as SAE).

Intensity and relationship of the AEs to vaccination as assessed by the investigator were also to be reported. The study duration for each study participant was approximately 6-8 months in Study DQIV-004, approximately 6 months in Study D-QIV-009 and 28 days (primed subjects) or 56 days (un-primed subjects) in Study D-QIV-015 for the 6 to 35 months cohort.

Causality of AEs: Assessed by *Investigator*. All solicited local (injection site) reactions were considered causally related to vaccination. The causal relationship, if any, between a specific solicited general AE and the administration of the study vaccine was evaluated by the Investigator using the following question:

'Was there a reasonable possibility that the AE was caused by the investigational product?'

NO: The AE was not causally related to administration of the study vaccine. There were other, more likely causes and administration of the study vaccine is not suspected to have contributed to the AE.

YES: There was a reasonable possibility that the vaccine contributed to the AE. Non-serious AEs and SAEs were evaluated as 2 distinct events. If an event met the criteria to be determined 'serious', it was examined by the Investigator to determine ALL possible contributing factors applicable to each SAE.

Severity/Intensity of AEs: Assessed by *Investigator*

Assessment of Intensity of AE

The investigator made an assessment of the maximum intensity that occurred over the duration of the event for all other AEs (including SAEs) reported during the study. The assessment was based on the Investigators' clinical judgement. The intensity of each AE was assigned to one of the following categories: 1 (mild) = easily tolerated, minimal discomfort and not interfering with everyday activities; 2 (moderate) = sufficiently discomforting to interfere with normal everyday activities; 3 (severe) = prevented normal, everyday activities. An event was defined as 'serious' when it met one of the pre-defined outcomes as described in the protocol.

Table 18: Intensity scales for solicited symptoms

Adverse event	Intensity grade	Parameter
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/ protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Redness at injection site		Recorded greatest surface diameter in mm
Swelling at injection site		Recorded greatest surface diameter in mm
Fever*		Recorded temperature in °C/°F
Irritability/Fussiness	0	Behaviour as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behaviour as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all
ORS†	0	Normal
	1	Mild: Easily tolerated
	2	Moderate: Interfered with normal activity
	3	Severe: Prevented normal activity

* Fever was defined as temperature $\geq 37.5^{\circ}\text{C}/99.5^{\circ}\text{F}$ in study D-QIV-009 and as temperature $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$ in studies D-QIV-004 and D-QIV-015. The preferred route for recording temperature was axillary.

† ORS recorded only in study D-QIV-015.

The maximum intensity of local injection site redness/swelling was scored at as follows:

Grade 0:	Absent
Grade 1:	≤ 20 mm
Grade 2:	> 20 mm to ≤ 50 mm
Grade 3:	> 50 mm

7.2. Studies providing evaluable safety data

7.2.1. Pivotal studies that assessed safety as the sole primary outcome

None.

7.2.2. Pivotal and/or main efficacy studies

Study D-QIV-004 (pivotal efficacy study).

7.2.3. Other studies

Supportive studies D-QIV-009 and -015.

7.3. Studies that assessed safety as the sole primary outcome

There were no studies in this application that assessed safety as the sole primary outcome.

7.4. Patient exposure in children 6 to 35 months of age

In D-QIV-004 and D-QIV-015 (6 to 35 months cohort) 6,006 and 474 subjects respectively, aged 6 to 35 months received at least one dose of Fluarix Tetra (Fluarix Tetra or Tetra Fluarix LP, manufacture according to the process licensed at time of study conduct). In Study D-QIV-009, 470 subjects aged 17 to 48 months received ≥ 1 dose of Fluarix Tetra of whom 241 subjects were previously primed in DQIV-004 and received a third dose. In Study D-QIV-015, 466 subjects received ≥ 1 dose of Fluarix Tetra manufactured according to the new harmonised process (Tetra Fluarix IP). A control vaccine (Havrix, Varivax/Varilrix or Prevnar) was administered to 6012 subjects in Study D-QIV-004. Overall, 12,714 doses of Fluarix Tetra

(manufacturing process licensed at time of study conduct) and 887 doses of Tetra Fluarix IP were administered to subjects 6 to 35 months of age in Studies D-QIV-004 and D-QIV-015. In Study D-QIV-009, 699 doses of Fluarix Tetra were administered to subjects 17-48 months of age.

7.5. Adverse events

7.5.1. All adverse events (irrespective of relationship to study treatment)

7.5.1.1. Integrated safety analyses

Given the significantly larger size and longer duration of Study D-QIV-004, the safety data from this study is considered to provide the foundation of the safety profile in children 6 to 35 months of age. Formal comparisons or pooling of data across the three studies provided in this application was not warranted due to the differences in control groups, the study populations and study durations.

7.5.1.2. Pivotal Study D-QIV-004

Any AE (solicited or unsolicited during the 7 day post-vaccination follow-up period)

At least one AE (any solicited or unsolicited, local or general) was reported for 51.8% (38.4% overall/dose) in the Fluarix Tetra group and 53.8% (39.7% overall/dose) in the control group. At least one Grade 3 AE was reported for 6.0% (3.2 overall/dose) in the Fluarix Tetra group and for 6.2% (3.4% overall/dose) in the control group. At least one possibly related AE was reported for 41.7% (30.5% overall/dose) in the Fluarix Tetra group and 43.9% 31.7% overall/dose) in the control group. At least one Grade 3 AE with causal relationship was reported for 3.8% (2.0% overall/dose) in the Fluarix Tetra group and for 3.9% (2.1% overall/dose) in the control group.

7.5.1.3. Other Studies D-QIV-009 and -015

D-QIV-009

Any symptom (local or general, solicited or unsolicited): During the 7 day follow-up post Dose 1, 59.8% and 57.2% of the subjects in the vaccine primed and vaccine-un-primed groups, respectively, had at least one symptom reported. Grade 3 symptoms were reported for 6.2% and 5.7% of the subjects, respectively.

D-QIV-015 Any AE (solicited or unsolicited) during the 7 day post-vaccination follow-up period in children 6 to 35 months of age

The frequency of reported AEs (any solicited or unsolicited, local or general) during the 7 day postvaccination follow-up period was similar between Tetra Fluarix IP and Tetra Fluarix LP groups in this per country analysis. The incidence of ≥ 1 solicited or unsolicited AE was highest in Spain, reported (overall per subject) for 82.2% (67.2% overall per dose) in the Tetra Fluarix IP group, and for 78.2% (63.3% overall per dose) in the Tetra Fluarix LP group. This was followed by Germany, where 80.4% (69.4% overall per dose) reported ≥ 1 solicited or unsolicited AE in the Tetra Fluarix IP group and 81.0% (70.1% overall per dose) in the Tetra Fluarix LP group. France reported ≥ 1 AE for 61.4% (45.6% overall per dose) in the Tetra Fluarix IP group and for 60.0% (44.0% overall per dose) in the Tetra Fluarix LP group. Poland reported ≥ 1 AE for 60.4% (51.0% overall per dose) in the Tetra Fluarix IP group and for 47.3% (37.0% overall per dose) in the Tetra Fluarix LP group. Bangladesh reported ≥ 1 AE for 11.1% (5.6% overall per dose) in the Tetra Fluarix IP group and for 18.0% (9.1% overall per dose) in the Tetra Fluarix LP group.

7.5.2. Treatment related adverse events (adverse drug reactions)

7.5.2.1. Pivotal Study D-QIV-004

Solicited local AEs (during the 7 day post-vaccination follow-up period) (Table 18)

Injection site pain was the most commonly reported solicited local AE during the 7 day post-vaccination period and was reported for 22.9% (15.6% overall/dose) in the Fluarix Tetra group and 23.3% (16.0% overall/dose) in the control group. There was no increase in the incidences of solicited local AEs from Dose 1 to Dose 2 of the Fluarix Tetra vaccine. Grade 3 solicited local AEs were not reported for more than 0.8% of subjects (0.4% overall/dose) in both vaccine groups.

Solicited general AEs (during the 7 day post-vaccination follow-up period) (Table 19)

The most commonly reported solicited general AE during the 7 day post-vaccination period was irritability/fussiness, reported for 23.4% (14.9% overall/dose) in the Fluarix Tetra group and 24.2% (15.5% overall/dose) in the control group. The most commonly reported solicited Grade 3 general AE during the 7 day post-vaccination period was fever (>39.0°C), reported for 2.3% of subjects (1.2% overall/dose) in the Fluarix Tetra group and 2.4% of subjects (1.3% overall/dose) in the control group.

Unsolicited AEs (during the 28 day post-vaccination follow-up period)

The % who reported ≥1 unsolicited AE of any grade during the 28 day follow-up period was 44.0% and 44.6% for the Fluarix Tetra and control groups, respectively: Nasopharyngitis (14.5% and 15.7% of subjects in the Fluarix Tetra and control groups respectively) and upper respiratory tract infection (URTI) (8.7% and 8.6% of subjects in the Fluarix Tetra and control groups, respectively) were most frequently reported. The % of subjects who reported the occurrence of Grade 3 unsolicited AEs was 2.7% (Fluarix Tetra) and 2.5% (Control). The % who reported the occurrence of unsolicited AEs that were possibly related to vaccination according to the investigator was 1.8% (Fluarix Tetra) and 1.9% (Control). Seven subjects (0.1%) in the Fluarix Tetra group and 3 subjects (<0/1%) in the Control group reported the occurrence of Grade 3 unsolicited AEs that were causally related to vaccination.

Unsolicited AEs with MAVs (during the entire study period)

The % who reported at ≥1 AE with MAV during the entire study period was 64.7% in the Fluarix Tetra group and 66.3% in the control group. Nasopharyngitis (29.0% and 30.0% of subjects in the Fluarix Tetra and control groups, respectively) and URTI (18.2% and 19.0% of subjects in the Fluarix Tetra and control groups, respectively) were most frequently reported. Grade 3 AEs with MAV were reported for 3.3% and 3.5% of subjects in the Fluarix Tetra and control groups, respectively. AEs with MAV with possible causal relationship to the vaccine according to the investigator were reported for 0.9% and 1.0% in the Fluarix Tetra and control groups, respectively. Four subjects (0.1%) in the Fluarix Tetra group and 2 subjects (<0.1%) in the control group reported at ≥1 Grade 3 MAE with causal relationship to vaccination.

Febrile convulsions

In Study D-QIV-004, 44 subjects experienced febrile convulsion over the entire study duration (21 subjects in the Tetra Fluarix group and 23 subjects in the control group). Of these, 28 cases were SAEs with 13 subjects reported SAEs in the Tetra Fluarix group and 15 subjects in the control group. Non-serious AEs of febrile convulsion were reported in 8 subjects in the Tetra Fluarix group and 8 subjects in the control group. All cases (serious and non-serious) of febrile convulsion were resolved. Within 28 days after vaccination, febrile convulsions were reported by 8 subjects in the Tetra Fluarix group (6 SAEs) and 7 subjects in the Control group (5 SAEs). Two subjects in the Tetra Fluarix group and 1 subject in the control group reported febrile convulsions with possible causal relationship to vaccination according to the Investigator (reported as SAEs). For 2 SAEs of febrile convulsion (2 days and 10 days post-vaccination) and 1

non-serious AE (1 day post-vaccination), a causal relationship to vaccination was not concluded by the sponsor due to confounding factors or incomplete information, but causality associated with vaccination could not be entirely ruled out.

Table 19: Incidence of solicited local symptoms reported during the 7 day (Days 0-6) post-vaccination period following each dose and overall for children 6-11 months of age (Total vaccinated cohort)

Symptom	Type	D-QIV					Control				
		N	n	%	95 % CI		N	n	%	95 % CI	
Dose 1											
Pain	All	621	92	14.8	12.1	17.9	620	187	30.2	26.6	33.9
	Grade 2 or 3	621	22	3.5	2.2	5.3	620	58	9.4	7.2	11.9
	Grade 3	621	2	0.3	0.0	1.2	620	13	2.1	1.1	3.6
	Medical advice	621	0	0.0	0.0	0.6	620	0	0.0	0.0	0.6
Redness (mm)	All	621	112	18.0	15.1	21.3	620	177	28.5	25.0	32.3
	>20	621	4	0.6	0.2	1.6	620	7	1.1	0.5	2.3
	>50	621	1	0.2	0.0	0.9	620	0	0.0	0.0	0.6
	Medical advice	621	1	0.2	0.0	0.9	620	0	0.0	0.0	0.6
Swelling (mm)	All	621	55	8.9	6.7	11.4	620	125	20.2	17.1	23.5
	>20	621	2	0.3	0.0	1.2	620	15	2.4	1.4	4.0
	>50	621	0	0.0	0.0	0.6	620	0	0.0	0.0	0.6
	Medical advice	621	0	0.0	0.0	0.6	620	0	0.0	0.0	0.6
Dose 2											
Pain	All	609	62	10.2	7.9	12.9	615	140	22.8	19.5	26.3
	Grade 2 or 3	609	11	1.8	0.9	3.2	615	40	6.5	4.7	8.8
	Grade 3	609	1	0.2	0.0	0.9	615	6	1.0	0.4	2.1
	Medical advice	609	0	0.0	0.0	0.6	615	0	0.0	0.0	0.6
Redness (mm)	All	609	72	11.8	9.4	14.7	615	124	20.2	17.1	23.6
	>20	609	0	0.0	0.0	0.6	615	9	1.5	0.7	2.8
	>50	609	0	0.0	0.0	0.6	615	0	0.0	0.0	0.6
	Medical advice	609	0	0.0	0.0	0.6	615	1	0.2	0.0	0.9
Swelling (mm)	All	609	38	6.2	4.5	8.5	615	88	14.3	11.6	17.3
	>20	609	0	0.0	0.0	0.6	615	11	1.8	0.9	3.2
	>50	609	0	0.0	0.0	0.6	615	3	0.5	0.1	1.4
	Medical advice	609	0	0.0	0.0	0.6	615	0	0.0	0.0	0.6
Overall/dose											
Pain	All	1230	154	12.5	10.7	14.5	1235	327	26.5	24.0	29.0
	Grade 2 or 3	1230	33	2.7	1.9	3.7	1235	98	7.9	6.5	9.6
	Grade 3	1230	3	0.2	0.1	0.7	1235	19	1.5	0.9	2.4
	Medical advice	1230	0	0.0	0.0	0.3	1235	0	0.0	0.0	0.3
Redness (mm)	All	1230	184	15.0	13.0	17.1	1235	301	24.4	22.0	26.9
	>20	1230	4	0.3	0.1	0.8	1235	16	1.3	0.7	2.1
	>50	1230	1	0.1	0.0	0.5	1235	0	0.0	0.0	0.3
	Medical advice	1230	1	0.1	0.0	0.5	1235	1	0.1	0.0	0.5
Swelling (mm)	All	1230	93	7.6	6.1	9.2	1235	213	17.2	15.2	19.5
	>20	1230	2	0.2	0.0	0.6	1235	26	2.1	1.4	3.1
	>50	1230	0	0.0	0.0	0.3	1235	3	0.2	0.1	0.7
	Medical advice	1230	0	0.0	0.0	0.3	1235	0	0.0	0.0	0.3
Overall/subject											
Pain	All	623	117	18.8	15.8	22.1	621	230	37.0	33.2	41.0
	Grade 2 or 3	623	31	5.0	3.4	7.0	621	85	13.7	11.1	16.6
	Grade 3	623	3	0.5	0.1	1.4	621	18	2.9	1.7	4.5
	Medical advice	623	0	0.0	0.0	0.6	621	0	0.0	0.0	0.6
Redness (mm)	All	623	126	20.2	17.1	23.6	621	217	34.9	31.2	38.8
	>20	623	4	0.6	0.2	1.6	621	15	2.4	1.4	4.0
	>50	623	1	0.2	0.0	0.9	621	0	0.0	0.0	0.6
	Medical advice	623	1	0.2	0.0	0.9	621	1	0.2	0.0	0.9
Swelling (mm)	All	623	75	12.0	9.6	14.9	621	168	27.1	23.6	30.7
	>20	623	2	0.3	0.0	1.2	621	22	3.5	2.2	5.3
	>50	623	0	0.0	0.0	0.6	621	3	0.5	0.1	1.4
	Medical advice	623	0	0.0	0.0	0.6	621	0	0.0	0.0	0.6

D-QIV = Subjects who received the Flu D-QIV Vaccine

Control = Subjects who received the Control vaccine (Havrix/Varivax/Varivax/Prevnar)

For each dose and overall/subject:

N = number of subjects with at least one documented dose

n/% = number/percentage of subjects reporting the symptom at least once

For Overall/dose:

N = number of documented doses

n/% = number/percentage of doses followed by at least one type of symptom

95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Table 20: Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7 day (Days 0-6) post-vaccination period following each dose and overall – by age strata (TVC)

	Group	Sub-group	Any symptom					General symptoms					Local symptoms				
			N	n	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
Dose 1	D-QIV	6-17 m	1920	690	35.9	33.8	38.1	1917	414	21.6	19.8	23.5	1919	472	24.6	22.7	26.6
		18-35 m	3983	1340	33.6	32.2	35.1	3981	667	16.8	15.6	18.0	3980	1005	25.3	23.9	26.6
	Control	6-17 m	1946	863	44.3	42.1	46.6	1946	524	26.9	25.0	29.0	1946	607	31.2	29.1	33.3
		18-35 m	3950	1239	31.4	29.9	32.8	3950	622	15.7	14.6	16.9	3950	918	23.2	21.9	24.6
Dose 2	D-QIV	6-17 m	1883	518	27.5	25.5	29.6	1882	310	16.5	14.8	18.2	1883	345	18.3	16.6	20.1
		18-35 m	3875	1005	25.9	24.6	27.3	3873	494	12.8	11.7	13.8	3874	771	19.9	18.7	21.2
	Control	6-17 m	1917	636	33.2	31.1	35.3	1916	390	20.4	18.6	22.2	1917	446	23.3	21.4	25.2
		18-35 m	3849	958	24.9	23.5	26.3	3846	485	12.6	11.6	13.7	3849	689	17.9	16.7	19.1
Overall/dose	D-QIV	6-17 m	3803	1208	31.8	30.3	33.3	3799	724	19.1	17.8	20.3	3802	817	21.5	20.2	22.8
		18-35 m	7858	2345	29.8	28.8	30.9	7854	1161	14.8	14.0	15.6	7854	1776	22.6	21.7	23.6
	Control	6-17 m	3863	1499	38.8	37.3	40.4	3862	914	23.7	22.3	25.0	3863	1053	27.3	25.9	28.7
		18-35 m	7799	2197	28.2	27.2	29.2	7796	1107	14.2	13.4	15.0	7799	1607	20.6	19.7	21.5
Overall/subject	D-QIV	6-17 m	1922	839	43.7	41.4	45.9	1922	561	29.2	27.2	31.3	1922	560	29.1	27.1	31.2
		18-35 m	3988	1627	40.8	39.3	42.3	3986	905	22.7	21.4	24.0	3985	1249	31.3	29.9	32.8
	Control	6-17 m	1949	1029	52.8	50.6	55.0	1949	709	36.4	34.2	38.6	1949	723	37.1	34.9	39.3
		18-35 m	3952	1564	39.6	38.0	41.1	3952	880	22.3	21.0	23.6	3952	1151	29.1	27.7	30.6

D-QIV = Subjects who received the Flu D-QIV Vaccine

Control = Subjects who received the Control vaccine (Havrix/Varivax/Varilrix/Prevnar)

6-17 m = Subjects 6 to less than 18 months of age

18-35 m = Subjects 18 to less than 36 months of age

For each dose and overall/subject:

N = number of subjects with at least one documented dose

n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered

For overall/dose:

N = number of documented doses

n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered

95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Pid 22406 of age 43 months at first vaccination from control group was included in age group 18-35 months

7.5.2.2. Other Studies D-QIV-009 and 015

D-QIV-009 Unsolicited adverse events

During the 28 day follow-up post Dose 1, ≥ 1 unsolicited AE was reported for 27.4% and 28.8% in the vaccine primed and vaccine-un-primed groups, respectively. Grade 3 unsolicited AEs were reported for 2.5% and 3.1% of the subjects and unsolicited AE with a causal relationship to vaccination for 2.1% and 1.3% of the subjects in the vaccine primed and vaccine-un-primed groups, respectively. ≥ 1 unsolicited AE with a medically attended visit during the 28 day follow-up post Dose 1 was reported for 20.3% and 21.4% of the subjects and during the entire study period for 61.8% and 56.8% of the subjects in the vaccine primed and vaccine-un-primed groups, respectively. Grade 3 unsolicited AE with a medically-attended visit was reported for 1.7% of the subjects in each group, during the 28 day follow-up post Dose 1 and for 2.1% and 3.5% of the vaccine primed and vaccine un-primed groups, respectively, during the entire study period. One unsolicited AE (URTI) with a medically attended visit assessed by the investigator as causally related to the vaccine was reported during the 28 day follow-up post Dose 1 for one subject in the vaccine-un-primed group. In this study, one febrile convulsion was reported for a vaccine primed male subject, aged 28 months at the time of vaccination. The febrile convulsion occurred 100 days after the study vaccination. The event was not considered an SAE, and was not related to the study vaccination, according to the investigator. The subject recovered without any sequelae.

D-QIV-015: Solicited AEs in children 6 to 35 months of age

Solicited local AEs included pain, redness and swelling at the injection site in children 6 to 35 months of age. During the 7 day follow-up period after each dose, redness and pain were the most frequently reported solicited local AEs. The incidence of solicited local AEs was similar between both groups in this per country analysis. In Bangladesh, where the completion of diary cards was done with assistance of a field worker, a lower incidence of solicited local AEs was

reported compared to other countries. Overall per subject in the Tetra Fluarix IP group, any injection site pain was reported for 1.1% of subjects in Bangladesh, 14.3% of subjects in France, 22.4% of subjects in Spain, 27.8% of subjects in Germany and 32.1% of subjects in Poland. The incidence of pain *did not increase* after the second dose in both groups, Tetra Fluarix IP and Tetra Fluarix LP. Solicited local AEs of Grade 3 were infrequent and rates were similar between Tetra Fluarix IP and Tetra Fluarix LP in this per country analysis.

Solicited general AEs included fever, irritability/ fuzziness, drowsiness and loss of appetite in children 6- 35 months of age. During the 7 day follow-up period after each dose, irritability/fuzziness, drowsiness and loss of appetite were the most frequently reported solicited general AE. The incidence of solicited general AEs was similar between both groups (Tetra Fluarix IP and Tetra Fluarix LP) in this per country analysis. Bangladesh reported a lower incidence of solicited general AEs compared to other countries. Overall per subject in the Tetra Fluarix IP group, fever of $\geq 38^{\circ}\text{C}$ (100.4°F) after Dose 1 or Dose 2 was reported for 4.4% of subjects in Bangladesh, 5.7% of subjects in Poland, 17.1% of subjects in France, 20.6% of subjects in Germany and 21.7% of subjects in Spain. Solicited general AEs of Grade 3 were infrequent and rates were similar between Tetra Fluarix IP and Tetra Fluarix LP in this per country analysis.

D-QIV-015 Unsolicited AEs in children 6 to 35 months of age

During the 28 day follow-up period after each dose, the % of subjects reporting at ≥ 1 unsolicited symptom was similar between the Tetra Fluarix IP and the Tetra Fluarix LP groups in this per country analysis. In the Tetra Fluarix IP group, the % of subjects reporting at ≥ 1 unsolicited symptom was 20.0% in Bangladesh, 20.8% in Poland, 53.1% in Germany, 59.2% in France and 77.9% in Spain. Unsolicited AEs with causal relationship to vaccination were infrequent and rates were similar between Tetra Fluarix IP and Tetra Fluarix LP in this per country analysis. The % of subjects reporting at ≥ 1 Grade 3 unsolicited AE was comparable between Tetra Fluarix IP and Tetra Fluarix LP groups.

7.5.3. Deaths, serious adverse events, pIMDs

7.5.3.1. Pivotal Study D-QIV-004

At least one SAE was reported for 3.6% of subjects in the Fluarix Tetra group and for 3.3% of subjects in the control group. There were 7 SAEs with causal relationship to vaccination reported for 6 subjects (0.1%) in the Fluarix Tetra group and 2 SAEs with causal relationship reported for 2 subjects ($<0.1\%$) in the control group. Four subjects experienced SAEs associated with a fatal outcome (1 subject in Fluarix Tetra group and 3 subjects in Control group). None of the SAEs associated with fatal outcome were attributed to the study vaccine.

Details of the deaths: The subject in the Tetra Fluarix group was a 20-month-old male child who died 23 days after receiving the first dose of Fluarix Tetra due to drowning. In the Control group, 2 subjects died due to drowning. One subject in the Control group died from complications of bronchitis, pneumonia and pleural effusion, 51 days after the second dose of control vaccine.

pIMDs (during the entire study period): In D-QIV-004, 5 subjects (0.08%) in the Tetra Fluarix group reported at least one pIMD and none in the control group. Three of the cases were possibly causally related to vaccination according to the Investigators (idiopathic thrombocytopenic purpura, facial paralysis and nephrotic syndrome), and 2 were not (coeliac disease, facial paralysis).

7.5.3.2. Other Studies D-QIV-009 and -015

D-QIV-009: SAE: A total of 15 subjects (7 [2.9%] in the vaccine primed group and 8 [3.5%] in the vaccine-un-primed group) reported 19 SAEs during the entire study period. No vaccine-related SAEs were reported during the study. No deaths.

pIMDs: No *pIMDs* were reported during the entire study period.

D-QIV-015: one occurrence of an SAE of febrile convulsion was reported in a subject from 6 to 35 months Cohort in the Tetra Fluarix LP group.

7.5.4. Discontinuations due to adverse events

7.5.4.1. Pivotal Study D-QIV-004

There were 3 subjects in the Fluarix Tetra group and 10 subjects in the control group who discontinued prematurely due to a non-serious AE; 1 subject in the Fluarix Tetra group and 6 subjects in the control group prematurely discontinued due to an SAE. One non-serious AE (URTI) in the Fluarix Tetra group) had a possible causal relationship to vaccination according to the investigator.

7.5.4.2. Other Studies D-QIV-009 and -015

D-QIV-009: withdrawals due to adverse events /serious adverse events: none.

D-QIV-015: Twenty subjects (7 in the Tetra Fluarix IP group and 13 in the DQIV LP group) were withdrawn from the study. The major reason was due to withdrawal of consent *unrelated to an adverse event*; 3 subjects were withdrawn for *non-serious* adverse events.

7.6. Issues with possible regulatory impact

7.6.1. Liver function, liver toxicity, renal function, renal toxicity, Other clinical chemistry, Haematology and haematological toxicity

Not assessed.

7.6.2. Electrocardiograph findings and cardiovascular safety

Not assessed.

7.6.3. Vital signs and clinical examination findings

Not assessed, aside from temperature, see under solicited systemic findings.

7.6.4. Immunogenicity and immunological events

None revealed. See details of *pIMD* in *D-QIV-004*.

7.6.5. Serious skin reactions

None revealed.

7.7. Other safety issues

7.7.1. Safety in special populations

Not assessed.

7.7.2. Safety related to drug-drug interactions and other interactions

Not assessed.

7.8. Post marketing experience

Fluarix Tetra has not been marketed for use in children below 3 years of age. The latest Periodic Risk Benefit Evaluation Report documents safety information of Fluarix Tetra collected through postmarketing surveillance in subjects as of 3 years of age from 16-Mar-2015 to 15-Mar-2016. Subject exposure to Fluarix Tetra from marketing experience is estimated to be 39,433,132 in the reporting period and 53,585,113 since launch, assuming that vaccination with Fluarix Tetra

follows a 1-dose schedule. Since first approval on 14 December 2012, no actions were taken for safety reasons regarding withdrawal, rejection, suspension or failure to obtain a renewal of a Marketing Authorization.

7.9. Evaluator's overall conclusions on clinical safety

The safety and reactogenicity profile of Fluarix Tetra was similar to well characterised licensed vaccines (including a live-attenuated varicella vaccine) used in the same age group in Study D-QIV-004. The rates of reported solicited and unsolicited symptoms were comparable between Fluarix Tetra recipients and non-influenza vaccine control recipient. No increase in reactogenicity was observed after the second dose. Safety data for Fluarix Tetra from studies the supporting Studies, D-QIV-009 and D-QIV-015 was fairly comparable. However, when a revaccination dose was given to primed subjects in D-QIV-009, a slight increase in reactogenicity in terms of reported solicited local symptoms was observed. As confirmed in D-QIV-015 the reactogenicity and safety between the two processes for vaccine manufacture, was similar confirming that the manufacturing change does not impact the safety in this age group. The occurrence of SAEs and unsolicited AEs was balanced between the Tetra Fluarix group and the control group in Study D-QIV-004. No safety concerns were identified in terms of unsolicited AEs and SAEs across the 3 studies included in this application. In summary, and overall, the safety profile of Fluarix Tetra was comparable to other widely-accepted licensed vaccines and the data showed that Fluarix Tetra is well tolerated in children 6 to 35 months of age.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of Fluarix Tetra in the proposed usage are:

Indication	
Benefits	Strengths and Uncertainties
<ol style="list-style-type: none"> The pivotal study is a very large clinical efficacy study in influenza RT-PCR positive subjects; conducted over multiple influenza seasons, in high and LMIC setting. The findings, confirm clinical benefit, immunogenicity (in a subset), implied economic and social benefit of Fluarix Tetra, in children aged 6 to 35 mths of age. Revaccination in primed children (D-QIV-009) seemed safe and immunogenic. 	<ol style="list-style-type: none"> It is uncertain how these clinical endpoints were validated, was there a 100% monitoring? Did GSK review supporting clinical documentation? I know all investigators were trained in the protocol, but there might still have been significant differences in clinical diagnosis. Strengths: very large pivotal study, conducting over multiple influenza seasons in high and LMIC countries, good gender and ethnicity mix, findings are representative for a vaccine that can be used globally in this age group. Provided additional safety data for other vaccines approved for use in this age group. The study design of D-QIV-004 is not a traditional one, in that most influenza vaccine licensing studies would compare one type of influenza vaccine (usually a TIV) against the QIV, with immunogenicity endpoints. However, I think the design is sound, and the study was properly

Indication	
Benefits	Strengths and Uncertainties
	powered as a clinical endpoint study.

8.2. First round assessment of risks

The risks of Fluarix Tetra in the proposed usage are:

Risks	Strengths and Uncertainties
<ol style="list-style-type: none"> 1. Potential for administration in those under the age of 6 months, for example premature infants. 2. Possible underreporting of some side-effects in some countries in which the study was conducted (for example, Bangladesh), notable in Study D-QIV-015 	<ol style="list-style-type: none"> 1. Some uncertainty that all the solicited local and systemic events were captured completely for example where documentation was obtained by field workers.

8.3. First round assessment of benefit-risk balance

Favourable, the clinical efficacy, immunogenicity and favourable safety profile are supportive of the benefit of vaccination with Fluarix Tetra in children 6 to 35 months of age.

8.4. First round recommendation regarding authorisation

The evaluator recommends authorisation.

9. Clinical questions

None.

9.1. Second round evaluation

No second round clinical evaluation was conducted as no clinical questions were raised. Further information was provided by the sponsor on 29 November 2017 regarding the RMP. The scope of these questions and responses are beyond the scope of this AusPAR.

10. Second round benefit-risk assessment

10.1. Second round assessment of benefits

As per first round assessment; favourable.

10.2. Second round assessment of risks

As per first round assessment.

10.3. Second round assessment of benefit-risk balance

Favourable, the clinical efficacy, immunogenicity and favourable safety profile are supportive of the benefit of vaccination with Fluarix Tetra in children 6 to 35 months of age.

10.4. Second round recommendation regarding authorisation

The evaluator recommends the authorisation for Fluarix Tetra vaccination use to be extended to include children 6 to 35 months of age.

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