Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for influenza virus haemagglutinin (vaccine)

Proprietary Product Name: Influvac Tetra

Sponsor: Mylan Pharma Pty Ltd

November 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au >.

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.
- The words (Information redacted), where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
AE	Adverse event
AESI	Adverse event of special interest
ASA	Australian-specific annex
CDC	Centers of Disease Control and Prevention
CHMP (CPMP)	Committee for Medicinal Products for Human Use
CI	Confidence Interval
eCRF	Electronic Case Report Form
EU	European Union
FAS	Full analysis sample
FDA	Food and Drug Administration
GBS	Guillain Barré syndrome
GCP	Good Clinical Practice
GMFIs	Geometric Mean Fold Increases
GMR	Geometric mean ratio
GMTs	Geometric Mean Titres
Gp	Group
HA	Haemagglutinin
HAI or HI	Haemagglutination Inhibition
IB	Investigator Brochure
ICH	International Conference on Harmonization
ILI	Influenza like Infection
IM	Intramuscular
IRI	Intercurrent respiratory infection
ITT	Intention to treat

Abbreviation	Meaning
IVV	influenza virus vaccine
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
NA	Neuraminidase
NCIs	New Chronic Illnesses
NH	Northern Hemisphere
NOCI	new onset of chronic illness
PI	Prescribing Information
Pop'n	Population
PP	Per protocol
PT	Preferred Term
QIV	Quadrivalent inactivated Influenza Vaccine
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SCF	Seroconversion Factor
SH	Southern Hemisphere
SOC	System Organ Class
SPR	Seroprotection Rate
SRH	Single radial haemolysis
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TGA	Therapeutic Goods Administration
TIV	Trivalent Inactivated Influenza Vaccine

Abbreviation	Meaning
TRAE	Treatment related adverse event
US	United States
VE	Vaccine efficacy
VN	Virus neutralisation
WHO	World Health Organization
Yrs	Years

1. Introduction

This is a submission by the sponsor to register Influvac Tetra for the prevention of influenza A and B in adults aged ≥ 18 years. The suspension for injection includes 4 inactivated, split influenza virus strains (15/15/15/15 µg (total 60 µg) per 0.5 mL), 2 type A strain subtypes and 2 type B strains from separate lineages as recommended by the Australian Influenza Vaccine Committee for that season. The submission includes 1 completed Phase III clinical study (Study INFQ3001) in adults in support of this application. The proposed indication is supported by and relies on the large trial database and post approval pharmacovigilance data of the trivalent vaccine Influvac trivalent vaccine which contains 3 viral strains (1 influenza A/H1N1 strain, 1 influenza A/H3N2 strain, and 1 influenza B strain). The latter was first registered in Australia in January 2002 for adult use; Influvac Junior was registered in July 2006. Since 2005 the vaccine is thiomersal free (preservative). In summary, the clinical development plan consists of 3 studies, with a planned number of 2940 subjects to be exposed to the quadrivalent influenza vaccine, of whom approximately 1540 will be adults and approximately 1400 will be children and adolescents. The paediatric development plan accounts for potential age related differences in immune response with respect to previous exposure to influenza (priming status) and therefore distinguishes between the age groups of 6 to 35 months (= non-primed, or naïve), 3 to 8 years (= primed and naïve children) and 9 to 17 years (considered primed/non-naïve); a staggered approach over sequential seasons will be followed.

Study INFQ3002 will include 1200 children in stable health in the age range 3 to 17 years with a randomisation ratio 2:1 for 3 to 8 years and 9 to 17 years, respectively. The treatment groups will be quadrivalent influenza vaccine, trivalent influenza vaccine Influvac with the marketed lineage B strain and trivalent influenza vaccine with the alternative lineage B strain to investigate the comparability of the immunogenicity with respect to the common strains contained in the quadrivalent and trivalent vaccines and assess overall safety. Approximately 400 children will be exposed to quadrivalent influenza vaccine, of which approximately 270 will be aged 3 to 8 years. The study is planned to start in the 2016/2017 Northern Hemisphere (NH) season.

Study INFQ3003 will include approximately 2000 non-primed children in the age group of 6 to 35 months to investigate the protective efficacy of quadrivalent influenza vaccine versus a non-influenza vaccine. Equal stratification is planned for 4 age ranges (6 to 11 months; 12 to 18 months; 19 to 24 months and 25 to 35 months). Half of the 1000 children will be exposed to quadrivalent influenza vaccine. The study is planned to start in the subsequent next northern hemisphere season, but may comprise 1 or 2 seasons, depending on the outcome of an interim analysis at the end of the first season, with a planned enrolment of approximately 1000 subjects in each season.

Post-authorisation, a dedicated clinical trial is foreseen to assess the immunogenicity of quadrivalent influenza vaccine in children suffering from mild to severe immune deficiency with different severity levels of immune suppression.

1.1. 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.

1.2. Dosage forms and strengths

Influvac Tetra is a quadrivalent influenza vaccine (surface antigen, inactivated) consisting of a clear, aqueous suspension packed in pre-filled syringes each containing 0.5 mL. The vaccine contains predominantly HA of 4 strains (2 x 'A'; 2 x 'B') of influenza virus in phosphate buffered saline, calcium and magnesium chloride buffers.

1.3. Dosage and administration

A single 0.5 mL dose annually intramuscularly (IM), for the prevention of influenza caused by Influenza Virus, Types A and B in persons aged ≥ 18 years.

2. Clinical rationale

2.1. Background

2.1.1. 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. In general, influenza resolves within 2 to 7 days, although symptoms of cough and malaise may be prolonged. However, for some population groups, notably the elderly and those with chronic diseases influenza can exacerbate underlying medical conditions and/or lead to secondary viral or bacterial pneumonia (Fiore; Rothberg). During influenza epidemics, there is an increased mortality risk among older adults (age > 65 years), people with chronic diseases, and very young children (age 0 to 12 months), as well as an increase in morbidity and hospitalisation because of influenza-associated complications (Fiore; Monto).

Influenza A and B cause most of human disease. Influenza A viruses are divided into subtypes based on 2 viral external proteins, the haemagglutinin (HA) and the neuraminidase (NA).

Of the influenza type A virus subtypes, the 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 2 distinct genetic lineages, Yamagata and Victoria. In terms of infection, influenza type A viruses have been isolated from several non-human species, including birds, horses, and swine, whereas influenza type B viruses almost exclusively affect humans.

The influenza A or B surface glycoprotein HA is the key antigen involved in attachment of the virus to receptors on respiratory epithelial cells, whereas the NA glycoprotein is involved in release of the virus from the cell surface. During infection, the virus stimulates production of antibodies in the serum (immunoglobulin G) and nasal secretions (immunoglobulin A) to these surface glycoproteins. High levels of virus type-specific antibodies are associated with protection from disease due to infections with homologous and closely related influenza virus trains (Hay; Fiore). 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 (Hay).

Influenza type A is capable of major antigenic shifts when a novel HA emerges from re-assortment with an animal influenza virus. Influenza B undergoes less rapid antigenic drift, that is, generally more stable, than influenza A. 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 (Beyer).

Influenza epidemics have been associated with the circulation of type A/H3N2, type A/H1N1, and type B viruses, either individually or together. 2 genetically distinct lineages of influenza B viruses have co-circulated since 1985 (Rota). The burden of infection is largely on school age children, young adults, and the elderly (Belshe). In the US, B viruses account for 24% of positive specimens and 34% of reported paediatric influenza deaths (Ambrose), however the incidence can vary dramatically between influenza seasons (range 1% to 60%) (www.euroflu.org). 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 (Grant; Olson). Influenza B causes morbidity and mortality in all age groups, however in children it appears to be a disproportionate cause of influenza related hospitalizations and deaths compared to the type A strains (Thompson).

Currently, based on viral surveillance data, an influenza B virus representing one of these 2 lineages is selected each year to be included in the annual vaccine. The cross protection against infection with one B lineage provided by immunisation with a vaccine derived from the other B lineage is uncertain, but expected to be low (Belshe). Predicting which lineage will predominate has been challenging, and in some seasons, there has been a mismatch between the lineage chosen for the vaccine and the predominant circulating influenza B virus lineage. In Europe from 2003 to 2004 through 2010, the predominant lineage of a given season differed from that contained in the vaccine in 4 out of 8 seasons and overall an estimated 58% of lab confirmed influenza B samples were of the lineage not included in the vaccine (Ambrose). Based on the demonstrated burden of influenza B, the limited cross-protection between the 2 influenza B lineages, and the inability to accurately predict which influenza B lineage will circulate, it may be expected that seasonal influenza vaccines will be improved by the inclusion of influenza B strains from both lineages. While a good antigenic match would still not be assured, this step would eliminate a mismatch in lineage between the vaccine strain and circulating strains.

2.1.2. Current treatment options

According to the WHO vaccination is the most effective way to prevent influenza and its complications and is the key public health approach in most countries around the world, including Australia. Prevention of influenza illness is achieved by annual prophylactic immunisation, the exact composition of which changes according to what are predicted to be the predominant A and B strain(s) circulating in either the Northern or Southern Hemispheres for that influenza season.

2.2. Clinical rationale

Each year in Australia, influenza infection affects somewhere between 5 to 10% of the general population and this can be up to 20% in some years. Among Australian patients aged ≥ 50 years, influenza is annually associated with > 3,000 deaths and > 13,500 hospitalisations (data from the immunise.health.gov.au website). According to the WHO, vaccination is the most effective way to prevent influenza and its complications.

2.2.1. Switch from trivalent to quadrivalent vaccine

The planned change from the trivalent to quadrivalent influenza vaccine is not associated with major changes in the general production process, and therefore no change in the safety profile is expected. Extensive clinical experience gained with Influvac (trivalent) for over ≥ 30 years is considered relevant for the development of the quadrivalent vaccine as the antigens of the influenza strains in both formulations are similar. In fact, both the Victoria and Yamagata B strain lineages, either one or the other, have been present in former Influvac formulations and the immunogenicity and safety has been extensively studied in clinical studies. For the currently

used thiomersal free trivalent formulation, the Yamagata lineage has been contained in the vaccine for 5 out of 10 seasons versus 5 seasons for the Victoria-lineage. The immunogenicity, safety and reactogenicity profiles were similar, therefore it is not expected that the combination of the 2 B strain lineages in the quadrivalent vaccine will result in a different immunogenicity and safety profile compared to trivalent Influvac. This view is strengthened by recent publications comparing the quadrivalent and trivalent formulations of other influenza vaccines (Greenburg 2013, 2014; Jain; Domachowske; Pepin; Langley). In these studies, reactogenicity and safety of the quadrivalent formulations was consistent with the established profiles of the corresponding trivalent formulations. In addition, the second B strain in the quadrivalent formulations did not impact immune responses elicited by the 3 strains contained in the trivalent formulations.

2.3. Evaluator's commentary on the background information

This background information provides the rationale for this product and aligns with other submissions for approved (in Australia) quadrivalent influenza vaccines; FluQuadri and Fluarix Tetra.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- A Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety;
- A pivotal Phase III randomised, multicentre, double blinded study to evaluate the quadrivalent vaccine versus 2 TIVs each containing one of the 'B' strains contained in the QIV.

3.2. Paediatric data

The submission does not include paediatric efficacy/safety data, although paediatric studies are ongoing and/or planned. See Section 1 (above) for ongoing/planned studies.

3.3. 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 submission were conducted in accordance with GCP.

3.4. Evaluator's commentary on the clinical dossier

The main objectives of the quadrivalent clinical development program were to demonstrate that the candidate quadrivalent vaccine provides superior immunogenicity compared to the marketed trivalent Influvac for the added B strain without affecting antibody responses to the other strains and without compromising the safety profile.

4. Pharmacokinetics

With respect to the nature of the product, clinical pharmacology data have not been assessed. The subunit influenza vaccine, as all vaccines, induces antibodies, which consecutively are responsible for the desired effect of the intervention, that is, protection against an infectious disease (principle of active vaccination). The constituents of the vaccine itself are phagocytosed at the site of injection. Therefore, specific interaction or pharmacokinetic studies have not been carried out in man.

5. Immunogenicity

Efficacy and safety data arising from the pivotal study (Study INFQ3001) is summarised in Sections 7 and 8 respectively of this document. A number of supportive immunogenicity studies have previously been reviewed by the TGA, and can be considered supportive of this submission.

5.1. Evaluator's overall conclusions on immunogenicity from the supportive studies

None of the supportive immunogenicity studies provide any data for a quadrivalent vaccine. All pertain to the immunogenicity and safety of trivalent vaccines containing 2 'A' strains of influenza and 1 'B' strain of influenza. Each vaccine contains 15 µg of HA per strain. These data are included because they show that the 'B' strain as a component of these trivalent vaccines were safe and immunogenic.

6. Dosage selection for the pivotal studies

The dosage selection for the addition B strain immunogen in Influvac Tetra was based upon the standard used in the TIV, that is, 15 µg of HA per strain.

7. Clinical efficacy (immunogenicity)

The pivotal Study INFQ3001is not an 'efficacy' study, instead the immunogenicity data derived is used as a surrogate for clinical efficacy. This is a standard approach in influenza vaccine studies. The study was designed according to the Guideline on Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005) and the scientific advice from an EU national competent authority for registration of QIV in the adult/elderly population.
Anti-haemagglutinin (HA) antibody response is an established correlate of protection against influenza in adults; therefore, HI titre was the primary outcome measure in this study. The study aimed to demonstrate the comparability of the immunogenicity of the shared strains contained in both the QIV and TIV formulations. Therefore, the primary objective was to demonstrate that the post-vaccination HI antibody responses with QIV for each of the shared strains were non-inferior to those with the TIVs. The non-inferiority margin was set at 1.5, which was in agreement with the scientific advice obtained from an EU national competent authority and was also in accordance with the margin recommended by FDA guidelines. As a secondary efficacy objective, the study aimed to demonstrate that the added B strain in QIV provided an antibody response superior to that with the TIV for the alternate B strain lineage. In addition, the immunogenicity of each of the strains in QIV and TIVs was further characterised by describing the derived serology parameters of seroconversion, and mean fold increase with respect to HI and VN antibody titres and by performing analyses in study population subsets

according to age and pre-existing antibody status. Furthermore, CMI values were described for a subset of subjects.

Central Lab performing the HI assays, in accordance with the guidelines indicated by EMA:

- Any HI result < 10 (= undetectable) was expressed as 5;
- Sera which have a titre ≥ 10 but < 40 are considered positive but not protective;
- Sera with a titre ≥ 40 are considered positive and protective.

7.1. Studies providing evaluable efficacy data

See above, the pivotal Study INFQ3001 provide indirect evidence of 'efficacy' through serological responses to the vaccine which have been determined, over time, and from multiple sources to have clinical efficacy either in protecting against influenza acquisition or attenuating the course of the infection if infection is not completely prevented through vaccination.

7.2. Pivotal or main efficacy studies

7.2.1. Study INFQ3001

This was 'A Phase III, randomised, double blind, active controlled study in adults to assess the safety and immunogenicity of the candidate quadrivalent influenza vaccine and its non-inferiority to trivalent influenza vaccine'.

7.2.1.1. Study design, objectives, locations and dates

Study design

A Phase III, randomised, double blind, active controlled study in adults to assess the safety and immunogenicity of the candidate quadrivalent influenza vaccine (distributed by the sponsor trading under a preferred business name) and its non-inferiority to trivalent influenza vaccine.

Primary objective

To demonstrate in subjects ≥ 18 years of age the non-inferiority of QIV with respect to post-vaccination geometric mean haemagglutinin inhibition (HI) antibody titres against the shared strains compared with the trivalent influenza vaccines (TIV) with either the B strain of the Victoria (TIV(Vic)) or the B strain of the Yamagata lineage (TIV(Yam)).

Secondary objectives

1. To demonstrate in subjects ≥ 18 of age the superiority of QIV to TIV(Vic) and TIV(Yam) with respect to post-vaccination geometric mean HI antibody titres against the alternate lineage B strain;
2. To describe the immunogenicity for HI and virus neutralisation (VN) antibody titres using the derived serology parameters seroconversion and geometric mean fold increase for each of the strains in QIV and TIV, in adults (≥ 18 to ≤ 60 years of age) and elderly (≥ 61 years of age);
3. To describe the immunogenicity for HI and VN antibody titres in study population subsets according to age and pre-existing antibody status for each of the strains in QIV and TIV.
4. To describe cell mediated immunity (CMI) values for a subset of subjects.

Safety objectives

To compare the reactogenicity and the safety of QIV with that of the TIV treatment arms in adults and elderly.

Locations

n = 20 sites (in Belgium, Germany, Hungary, Latvia and Lithuania)

Dates

First subject, first visit: 28 May 2015; last subject last visit: 6 January 2016.

Protocols

Version 1 dated 11 November 2014; Amendment 1: 28 April 2015, key changes:

- Change 1: Russia excluded from participation. The study will be conducted solely in countries within Europe. Rationale: due to additional data requirements in Russia it was not feasible to obtain timely study approvals for conducting the study including Russian sites;
- Change 2: Subjects who have been placed in an institution by regulatory or legal ordinance are to be excluded from study participation. Rationale: it was requested by a Central Ethics Committee to exclude subjects that are in an institution by regulatory or legal ordinance;
- Change 3: acceptable methods of birth control should be in accordance with local regulations and that more stringent criteria may apply. Rationale: acceptable methods of birth control have been defined in the protocol under exclusion criteria;
- Change 4: Upon Competent Authority (CA) request the period of pregnancy reporting is extended beyond the immunisation phase. All pregnancy cases will be reported if they occur during the study, including the entire safety follow-up period. Rationale: Pregnancy is excluded per protocol during the first 3 weeks of the study to avoid any potential safety concern related to the vaccination. Any pregnancy occurring during the entire study duration including the safety follow-up period will be reported and followed on pregnancy evolution and outcome, that is, the health status of the newborn;
- Change 5: Specific reference is made to the safety reference information described in the Investigators' Brochure (IB);
- Change 6: Definition of seroconversion added to the statistical section of the protocol. Rationale: requested by a CA to add the definition of seroconversion to the protocol. That is, the following summary statistics will be presented, for each of the 4 strains and each of the 3 formulations: the pre and post vaccination geometric mean titres (GMTs) and the geometric mean fold increases for HI and VN; reverse cumulative distribution curves supplemented by tables presenting % of vaccinees with titres above cut-off on a logarithmic scale for HI and VN; seroconversion rates for HI and VN defined as becoming seropositive if seronegative at enrolment, or (at least) a 4 fold rise in titre if seropositive at enrolment.

7.2.1.2. Inclusion and exclusion criteria

Inclusion criteria

1. Gives informed consent and able to adhere to all study procedures;
2. Men and women aged ≥ 18 years of age at the day of study vaccination;
3. Being in good health as judged by medical history, physical examination and clinical judgment of the investigator.

Exclusion criteria

1. History of allergy to egg, chicken proteins, or other vaccine components;
2. History of serious adverse reaction to any influenza vaccine;
3. History of Guillain-Barré syndrome;

4. Confirmed influenza infection or vaccination against influenza in the 6 months preceding enrolment;
5. Receipt of any vaccine within the preceding 4 weeks prior to study vaccination or planned vaccination during the study between Visit 1 (Day 1) and Visit 2 (Day 22);
6. Having fever (oral temperature of ≥ 38.0 ºC) and/or presenting with an acute disease or infection on the day of study vaccination;
7. Any known immunocompromising condition or immunosuppressive therapy within 6 months preceding study vaccination;
8. Using or having used immunomodulating agents during the 4 weeks prior to the study or planned use during the study;
9. Receipt of blood or blood products within the 3 months preceding enrolment;
10. Participation in a placebo-controlled influenza vaccine clinical trial any time prior to entering this study if the treatment arm is not known;
11. Any condition that in the opinion of the investigator would pose a health risk to the subject if enrolled or could interfere with the evaluation of the study vaccine including (but not limited to) bleeding disorder, known immunodeficiency, seizure disorder, acute, severe or progressive hepatic, renal, neurological or neuromuscular disease;
12. Being a solid organ or bone marrow/stem cell transplant recipient;
13. Use of cytotoxic drugs, anticancer chemotherapy or radiation therapy within 36 months before the day of study vaccination;
14. Receipt of another investigational agent within 30 days prior to study vaccination, or planned use during the entire study period;
15. Known drug or alcohol abuse;
16. Planned surgery requiring a general anaesthetic, or surgery requiring inpatient hospitalisation for at least 24 hours during the entire study period;
17. Being an employee of the sponsor/contract research organisation conducting this study or personnel of the study site;
18. Any other reason that, in the investigator's opinion, prohibits the inclusion of the subject into the study;
19. Exclusion criteria only for female subjects aged ≥ 18 and ≤60 years and of childbearing potential: Being pregnant, breastfeeding or intending to become pregnant during the study period up to Visit 2 (Day 22);
20. Not using an acceptable method (as listed in the protocol) of birth control up to Visit 2 (Day 22).

7.2.1.3. Study treatments

Test product, dose and mode of administration

A single 0.5 mL dose of quadrivalent influenza subunit vaccine (with the strains recommended for the past influenza season NH2014/2015) was given. The HA content of the QIV batch as follows:

- A/California/7/2009 (H1N1) pdm09 like strain (A/California/7/2009, X-181) (16.9 µg HA/dose)
- A/Texas/50/2012 (H3N2) like strain (A/Texas/50/2012, X-223A) (17.0 µg HA/dose)

- B/Massachusetts/2/2012 like strain (B/Massachusetts/2/2012, BX-51B) (15.3 µg HA/dose)
- B/Brisbane/60/2008 (wild type) (17.3 µg HA/dose)

Reference therapy, dose and mode of administration

A single 0.5 mL dose of licensed Influvac containing approximately 15 µg of HA antigen per virus strain, or a single 0.5 mL dose of TIV containing the alternate B strain (both vaccines with the strains recommended for the past influenza season NH2014/2015), administered by intramuscular injection in the deltoid muscle of the upper arm.

The HA content of the $TIV_{(Vic)}$ batch was as follows:

- A/California/7/2009 (H1N1) pdm09 like strain (A/California/7/2009, X-181) (16.7 µg HA/dose)
- A/Texas/50/2012 (H3N2) like strain (A/Texas/50/2012, X-223A) (16.5 µg HA/dose)
- B/Brisbane/60/2008 (wild type) (18.4 µg HA/dose)

The HA content of the $TIV_{(Yam)(}$ Influvac) batch was as follows:

- A/California/7/2009 (H1N1) pdm09 like strain (A/California/7/2009, X-181) (17.1 µg HA/dose)
- A/Texas/50/2012 (H3N2) like strain (A/Texas/50/2012, X-223A) (16.6 µg HA/dose)
- B/Massachusetts/2/2012 like strain (B/Massachusetts/2/2012, BX-51B) (14.9 µg HA/dose)

Above mentioned HA doses are according to the respective certificates of analysis.

7.2.1.4. Efficacy variables and outcomes

Randomised, double blind, active controlled immunogenicity study in 2 age groups: adults and elderly. In both age groups, eligible participants will be randomly assigned to vaccination with QIV, $TIV_{(Vic)}$ or $TIV_{(Yam)}$, in a 7:1:1 ratio, respectively.

Screening performed at Visit 1, or alternatively maximally 2 weeks before: informed consent and review of medical history, inclusion and exclusion criteria, demographic data, concomitant medication, influenza and influenza vaccination history; physical examination.

Visit 1 (Day 1): pregnancy test for females of childbearing potential; assessment of AEs and concomitant medications; blood sampling for baseline immunogenicity assessment. Subjects were vaccinated with the study vaccine IM in the deltoid muscle of the arm. Subjects observed for ≥ 30 minutes to monitor for any immediate adverse reactions, and a daily diary, thermometer, and ruler provided for daily reporting of solicited local and systemic reactions and overall inconvenience occurring during the first 7 days after vaccination.

Subjects were instructed to report intercurrent respiratory infections immediately (that is, occurrence of symptoms or signs likely to predict influenza infection) in the period following vaccination until Visit 2 (Day 22) by phone contact, at which an extra visit was to be scheduled, preferably within 24 hours, but no later than 72 hours after the onset of symptoms. At these extra visits, a nasal and/or pharyngeal swab was to be collected for the diagnosis of influenza infection.

A telephone call occurred approximately 3 days after vaccination (Phone contact 1, Day 4) to ensure correct completion of the daily diary, to assess unsolicited AEs, use of concomitant medication and remind the subject to report potential intercurrent respiratory infections.

Visit 2 (Day 22) occurred 3 weeks after vaccination and included collection of the daily diary, assessment of AEs, concomitant medication, a symptom-directed physical examination if AEs

are present, pregnancy test for females of childbearing potential and blood collection for immunogenicity assessments.

A final telephone call occurred approximately 6 months after vaccination (Phone contact 2, Day 183) for recording any new SAEs and New Chronic Illnesses (NCIs) and any vaccinations received since Visit 2 (Day 22).

Primary endpoint(s)

Post-vaccination geometric mean HI antibody titres against the 2 A and the 2 B strains

Secondary endpoint(s)

Pre-vaccination geometric mean HI titres against the 2 A and the 2 B strains; pre- and post-vaccination geometric mean VN titres for a subset of subjects; seroconversion rates and geometric mean fold increases for HI and VN. Pre- and post-vaccination cell-mediated immunity (CMI) values for a subset of subjects.

Safety information captured

- Unsolicited (that is, spontaneously reported) AEs and SAEs following vaccination between Visit 1 (Day 1) and Visit 2 (Day 22). New SAEs and NCIs between Visit 2 (Day 22) and Phone contact 2 (Day 183).
- Solicited injection site reactions (that is erythema, swelling, induration, vaccination site pain, ecchymosis) and systemic reactions (that is fever, headache, malaise, myalgia, arthralgia, fatigue, sweating, shivering), within 7 days following vaccination.
- Overall inconvenience after the vaccination assessed.

7.2.1.5. Randomisation and blinding methods

Randomisation

Subjects assigned to a treatment group by means of randomisation using a centralised electronic system (interactive voice/web response system; IXRS). Randomisation was stratified by centre and age group. The IXRS assigned a 5 digit randomisation number to each subject according to a randomisation scheme. The medication was identified using 6 digit kit randomisation number. Randomisation scheme was provided by the sponsor's clinical supply management (drug product development department).

Blinding

Packaging and labelling was controlled by the sponsor's clinical supply chain management (product development and support). A sponsor-designated qualified person released all clinical supplies prior to shipment to investigational sites. A certificate of compliance was issued stating the expiry date of the clinical supplies. Distribution of study vaccine was done by a separate company. Blinded and packaged medication was provided to the investigational site and dispensed to the subjects. All syringes were identical in appearance, and packaged in the proper proportion to assure desired dosages and maintenance of blinding.

7.2.1.6. Analysis populations

All subjects consented sample = all subjects who gave their informed consent.

All subjects vaccinated sample = all subjects consented sample; and were vaccinated.

Safety sample = the all subjects vaccinated sample; and ≥ 1 post-vaccination safety observation.

Full analysis sample (FAS) = all subjects in the safety sample; and ≥ 1 post-vaccination efficacy observation.

Per-protocol sample defined through blind data review, and consists of all subjects who: are included in the FAS; and did not present any major protocol violation.

7.2.1.7. Sample size

Randomised, double blind, active controlled immunogenicity study in adults, stratified 1:1 for age in a non-elderly (≥ 18 to ≤60years) and an elderly (≥ 61 years) group. In both age groups, eligible participants randomly assigned to vaccination with QIV, $TIV_{(Vic)}$ or $TIV_{(Yam)}$, in a 7:1:1 ratio, respectively. The number of subjects to be allocated to treatment totals 1,980: 1,540 QIV: 220 $TIV_{(Vic)}$:220 $TIV_{(Yam)}$. Numbers of subjects to be screened was approximately 2,080 allowing for an approximate 5% screen failure rate. The proposed sample size was based on the scientific advice obtained from an EU National Competent Authority to collect safety data for an adequate number of subjects vaccinated with QIV. Given this, a sample size of 1,540 subjects vaccinated with QIV and 2 x 220 subjects vaccinated with TIV secures an overall statistical power of > 95% to demonstrate the non-inferiority of QIV to TIV with respect to the immunogenicity against the shared strains. The sample size provides further an overall statistical power of > 95% to demonstrate the superiority of QIV to TIV with respect to the induced immunogenicity against the alternate lineage B strain.

Table 1: Sample size calculations in Study INFQ3001

	QIV	$TIV_{(Yam)}$	$TIV_{(Vic)}$	Total
Adults (≥ 18 to ≤ 60 years of age)	770	110	110	990
Elderly (≥ 61 years of age)	770	110	110	990
Total	1,540	220	220	1,980

7.2.1.8. Statistical methods

Efficacy

Analysed for the FAS and the PP samples.

Primary efficacy

Non-inferiority of QIV to TIV with respect to the induced immunogenicity against the shared strains will be tested by comparing the Day 22 geometric means of the HI titres against these strains between the QIV and ITVs. For the A (H1N1) and the A (H3N2) strains the HI antibody titre data of the subjects vaccinated with a TIV will be pooled. Non-inferiority will be inspected by calculating for each of the 2 A strains and each of the 2 B strains a 2 sided 95% CI for geometric mean ratios (GMRs) for the contrast TIV versus QIV, using an analysis of variance model for the log-transformed titres, with age group and centre as factors in the model. The non-inferiority margin has been set to 1.5 in agreement with scientific advice obtained from an EU National Competent Authority. Non-inferiority of QIV to TIV will be concluded if for all 4 strains the upper limit of the 95% CI falls below 1.5. For this analysis the PP set will be the primary one.

Secondary efficacy

The superiority of QIV to TIV with respect to the induced immunogenicity against the alternate-lineage B strains will be tested by comparing the Day 22 geometric means of the HI titres against the alternate-lineage B strains between the QIV and the 2 TIVs. Both comparisons will be done at the 2-sided significance level 0.05. Summary statistics presented, for each of the 4 strains and each of the 3 formulations: the pre and post vaccination GMTs and the geometric mean fold increases for HI and VN; reverse cumulative distribution curves supplemented by tables presenting % of vaccinees with titres above cut-off on a log scale for HI and VN; seroconversion rates for HI and VN. In addition, analyses in subsets according to age and pre-existing antibody status presented. CMI values summarised.

Safety

Safety data analysed for the safety set, constituted by all vaccinated subjects. Safety data of the subjects vaccinated with a trivalent formulation was pooled. All safety analyses were done by

age group. Reporting rates of local and systemic reactions compared between the QIV and the TIV formulations by calculating 2 sided 95% CI for the relative risks (quadrivalent versus trivalent). The same analysis repeated on the numbers of subjects with ≥ 1 treatment emergent adverse event (TEAE), overall, and by MedDRA System Organ Class (SOC).

7.2.1.9. Participant flow

Figure 1: Flowchart of subject disposition in Study INFQ3001

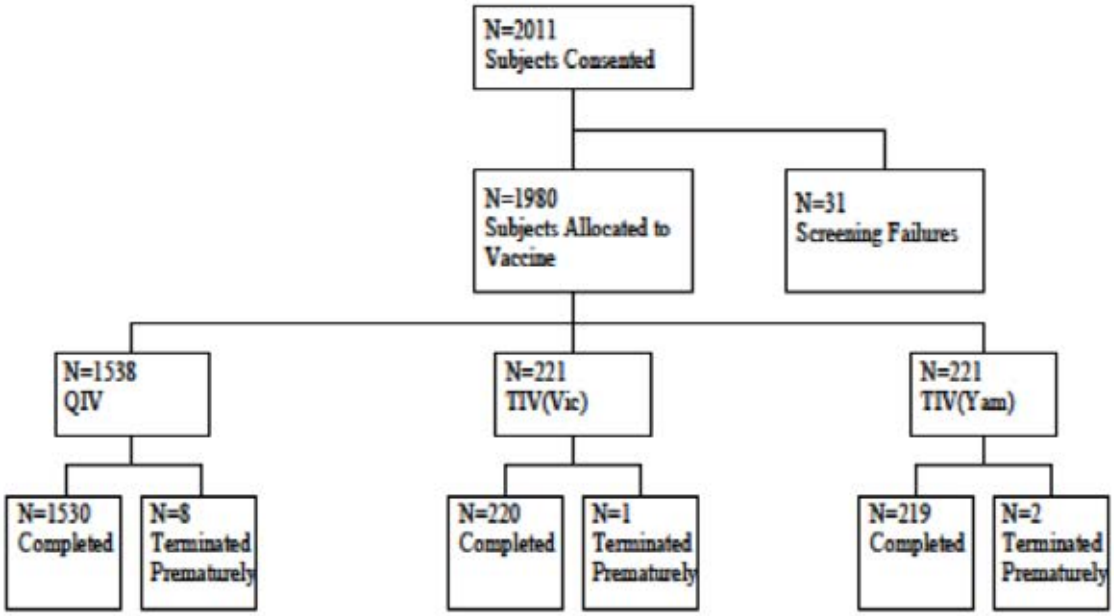
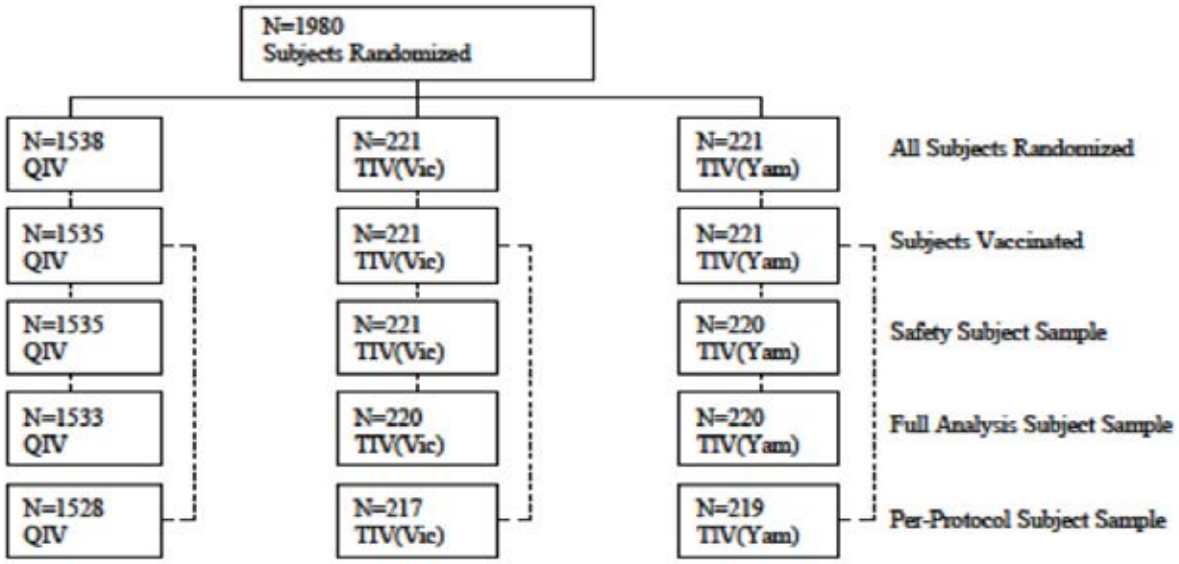


Figure 2: Flowchart of subject analysis populations in Study INFQ3001



7.2.1.10. Major protocol violations/deviations

Table 2: Subjects with critical or major protocol deviations in Study INFQ3001

Trial Arm	Category of Deviation	Major Protocol Deviation Specification
TIV(Yam)	MISSING POST-BASELINE DATA	Subject did not have phone contact on Day 4.
QIV	VIOLATION OF EXCLUSION CRITERIA	
QIV	POSSIBLE INTERCURRENT INFECTION	IRI occurred and no swab taken
TIV(Yam)	POSSIBLE INTERCURRENT INFECTION	IRI occurred and no swab taken
QIV	USE OF FORBIDDEN MEDICATION	Subject used systemic Medrol
TIV(Vic)	DATE OF PREVACCINATION BLOOD SAMPLING 5 DAYS BEFORE DATE OF VACCINATION	
TIV(Vic)	DATE OF PREVACCINATION BLOOD SAMPLING 10 DAYS BEFORE DATE OF VACCINATION	
QIV	WITHDREW PRIOR TO VACCINATION	
TIV(Vic)	MISSING EFFICACY DATA	Subject withdrew prior to Day 22
QIV	MISSING EFFICACY DATA	No Day 22 blood sample as subject died
QIV	WITHDREW PRIOR TO VACCINATION	
QIV	WITHDREW PRIOR TO VACCINATION	
QIV	POSSIBLE INTERCURRENT INFECTION	
TIV(Vic)	VIOLATION OF EXCLUSION CRITERIA	
QIV	UNRELIABLE IMMUNOGENICITY DATA	
QIV	USE OF FORBIDDEN MEDICATION	Subject used systemic corticosteroid

The highest proportion of subjects with major protocol deviations was observed in the categories of possible intercurrent infection and withdrawal prior to vaccination (3 subjects each, 0.2%)

7.2.1.11. Baseline data

Table 3: Demographics; All subjects randomised sample in Study INFQ3001

	Statistic	QIV (N = 1538)	$TIV_{(Vic)}$ (N = 221)	$TIV_{(Yam)}$ (N = 221)	All Subjects (N = 1980)
Age (years)	N	1538	221	221	1980
	Mean (SD)	55.9 (17.6)	55.4 (18.0)	55.0 (17.6)	55.7 (17.7)
	Median	61.0	61.0	60.0	61.0
	Min/Max	18/91	18/88	18/86	18/91
Age category (years)					
Adults (≥ 18 to ≤ 60)	n (%)	769 (50.0)	110 (49.8)	112 (50.7)	991 (50.1)
Elderly (≥ 61)	n (%)	769 (50.0)	111 (50.2)	109 (49.3)	989 (49.9)
Gender	N	1538	221	221	1980
Male	n (%)	664 (43.2)	100 (45.2)	95 (43.0)	859 (43.4)
Female	n (%)	874 (56.8)	121 (54.8)	126 (57.0)	1121 (56.6)
Race	N	1538	221	221	1980
White	n (%)	1529 (99.4)	221 (100.0)	221 (100.0)	1971 (99.5)
Asian	n (%)	3 (0.2)	0	0	3 (0.2)
Black or African American	n (%)	3 (0.2)	0	0	3 (0.2)
Other	n (%)	3 (0.2)	0	0	3 (0.2)

Abbreviations: Max = maximum; Min = minimum; QIV = quadrivalent influenza vaccine; SD = standard deviation; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.
Note: Percentages are based on the number of subjects in the all subjects-randomized sample with data.
For each subject one or more race categories could be selected.

As shown in Table 3 above, the majority of subjects were White (99.5%); 43.4% were male and 56.6% female. The mean (SD) age at screening was 55.7 (17.7) years. Adults had a mean age of 39 (SD = 12.6) years and a median age of 39 years (range: 18 to 60 years). About half of the adults were male. Elderly adults had a mean age of 69 (SD = 6.3) years and a median age of 68 years (range: 60 to 92 years). The proportion of adult and elderly subjects was similar in each vaccination group. In general, subject demographics were similar in all vaccination groups. The majority of subjects across vaccination groups had not previously received a vaccine against seasonal influenza (51.2% in the QIV group, 54.3% in the $TIV_{(Vic)}$ group, and 52.9% in the $TIV_{(Yam)}$ group) and had not experienced an ILI since the start of the last season (99.2% in the QIV group, 99.5% in the $TIV_{(Vic)}$ group, 99.1% in the $TIV_{(Yam)}$ group). The proportion of subjects who had previously received a seasonal influenza vaccine was higher in elderly subjects (61.2%

in the QIV group, 59.5% in the $TIV_{(Vic)}$ group, and 57.8% in the $TIV_{(Yam)}$ group) than in adult subjects (36.4% in the QIV group, 31.8% in the $TIV_{(Vic)}$ group, and 36.6% in the $TIV_{(Yam)}$ group).

7.2.1.12. Results for the primary efficacy outcome

For all 4 strains the upper limit of the 95% CI for the HI geometric mean ratio (GMR; TIV versus QIV) fell below the predefined non-inferiority margin of 1.5, meaning that the non-inferiority of QIV to TIV was demonstrated as shown in Table 4, below.

Table 4: Non-inferiority of QIV versus TIV against shared strains based on post-vaccination geometric mean HI titres; PP sample

Strain	QIV		TIV[a]		TIV[a]/QIV
	N	GMT	N	GMT	Adjusted GMR (95% CI)
A(H1N1)	1511	186.6	433	220.9	1.18 (1.023, 1.370)
A(H3N2)	1524	393.1	436	413.5	1.06 (0.928, 1.213)
		QIV		$TIV_{(Vic)}$	$TIV_{(Vic)}$/QIV
B-Victoria	1521	152.9	215	142.0	0.88 (0.726, 1.071)
		QIV		$TIV_{(Yam)}$	$TIV_{(Yam)}$/QIV
B-Yamagata	1520	102.1	215	86.1	0.82 (0.677, 0.998)

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; HI = hemagglutinin inhibition; N = number of subjects with nonmissing data; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.

[a] HI titer data of the two trivalent formulations were pooled for the two A-strains.

Note: Adjusted GMR and 95% CI were calculated using analysis of variance on the log-transformed titers at the Day 22 visit with age group, country, center, and vaccine group included as factors in the model.

Note: Noninferiority of QIV to TIV could be concluded if for all four strains the upper limit of the 95% CI fell below 1.5.

The primary efficacy analysis was repeated for the FAS and results were similar to the PP subject sample. The pre- and post-vaccination GMTs for HI were analysed in the 2 age groups and results demonstrated the comparability of GMTs between QIV and TIV per age group (Table 5).

Table 5: Geometric mean HI titres by strain; FAS

	A(H3N2)-strain		A(H1N1)-strain	
Statistic	QIV (N=768)	TIV* (N=222)	QIV (N=768)	TIV* (N=222)
Pre-vaccination (Day 1)				
n	764	222	759	218
GMT (GSD)	70.0 (5.55)	52.4 (5.37)	37.3 (5.18)	33.1 (5.04)
Post-vaccination (Day 22)				
n	766	222	759	220
GMT (GSD)	442.4 (3.18)	473.5 (3.73)	272.2 (3.71)	310.1 (3.87)

Note: n = Number of subjects with non-missing data; GMT = Geometric Mean Titer; GSD = Geometric Standard Deviation.
Note: *HI titer data of the two trivalent formulations pooled for the two A-strains.
Source: HIT005.SAS, PPD. Run 25MAY2016 11:41
Abbott Protocol INFQ3001

7.2.1.13. Results for other efficacy outcomes

For both B strain lineages, the HI GMT of the TIV group was less than half of the GMT in the QIV group: 64.1 versus 153.1 (B Victoria lineage) and 47.2 versus 101.9 (B Yamagata lineage) (Table 6). Both differences were statistically significant ($P < 0.0001$, both comparisons). Thus, the HI antibody responses elicited by the B strain antigens were superior to the antibody responses elicited by cross reactivity antigens of the alternate B strain lineages. The secondary efficacy analysis was repeated for the PP subject sample and was similar to the FAS.

Table 6: Superiority of QIV versus TIV against the alternate lineage B strains based on the post-vaccination geometric mean HI titres; FAS

Strain	QIV		TIV		TIV/QIV	
	N	GMT	N	GMT	Adjusted GMR (95% CI)	P value
		QIV		$TIV_{(Yam)}$	$TIV_{(Yam)}$/QIV	
B-Victoria	1526	153.1	218	64.1	0.41 (0.334, 0.493)	< 0.0001
		QIV		$TIV_{(Vic)}$	$TIV_{(Vic)}$/QIV	
B-Yamagata	1525	101.9	220	47.2	0.45 (0.374, 0.552)	< 0.0001

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; N = number of subjects with nonmissing data; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.

Note: Adjusted GMR and 95% CI were calculated using analysis of variance on the log-transformed titers at the Day 22 visit with age group, country, center, and vaccine group included as factors in the model.

GMTs by strain, ~~centre, country~~, and fold increase

In all vaccination groups, the HI antibody responses declined with increasing age for all 4 strains. In both adult subjects and elderly subjects, GMTs increased in all vaccination groups for the FAS from Day 1 (pre-vaccination) to the Day 22 visit after vaccination for all 4 strains. Both B strain lineages induced limited cross-reactivity. In the $TIV_{(Yam)}$ group, the GMTs for HI against the B Victoria lineage increased from 17.7 to 85.1 in the adult subjects and from 21.4 to 48.0 in the elderly subjects whereas the GMTS for the B-Yamagata lineage increased from 15.8 to 184.7 in the adult subjects and from 17.0 to 106.6 in the elderly subjects. Similarly, in the $TIV_{(Vic)}$ group, the GMTs for HI against the B-Yamagata lineage increased from 26.3 to 81.7 in the adult subjects and from 13.3 to 27.3 in the elderly subjects whereas the GMTS for the B-Victoria lineage increased from 20.2 to 128.7 in the adult subjects and from 16.4 to 57.4 in the elderly subjects. In both adult subjects and elderly subjects, the GMFIs in HI titres were similar across vaccination groups for all 4 strains. In the adult subjects (see Table 7, below), the Geometric Mean Fold Increases (GMFIs) varied between 6.3 and 11.4 in the QIV group and between 6.2 and 11.7 in the TIV groups (excluding alternate lineages). In the elderly subjects (see Table 8, below) the GMFIs varied between 4.2 and 5.5 in the QIV group and between 2.1 and 6.9 in the TIV groups (excluding alternate lineages). The GMFI in HI titres was repeated for the PP subject sample and were similar to the FAS.

Table 7: GMFIs in HI Titres; FAS (Adults)

	A(H3N2)-Strain		A(H1N1)-Strain		B-Strain Victoria Lineage			B-Strain Yamagata Lineage		
Statistic	QIV (N = 768)	TIV[a] (N = 222)	QIV (N = 768)	TIV[a] (N = 222)	QIV (N = 768)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 112)	QIV (N = 768)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 112)
Postvaccination										
n	764	222	758	218	758	110	109	763	110	109
GMFI (GSD)	6.3 (5.36)	9.0 (6.34)	7.3 (5.27)	9.4 (5.50)	11.4 (5.00)	11.7 (6.12)	4.8 (4.19)	6.8 (4.58)	3.1 (3.97)	6.2 (4.85)

Abbreviations: GMFI = geometric mean fold increase; GSD = geometric standard deviation; HI = hemagglutinin inhibition; n = number of subjects with nonmissing data; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.

[a] HI titer data of the two trivalent formulations pooled for the two A-strains.

Table 8: Geometric mean fold increases in HI titres; FAS (Elderly)

	A(H3N2)-Strain		A(H1N1)-Strain		B-Strain Victoria Lineage			B-Strain Yamagata Lineage		
Statistic	QIV (N = 765)	TIV[a] (N = 218)	QIV (N = 765)	TIV[a] (N = 218)	QIV (N = 765)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 108)	QIV (N = 765)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 108)
Postvaccination										
n	761	218	755	216	759	108	108	758	110	106
GMFI (GSD)	4.2 (4.80)	4.8 (5.21)	5.2 (4.69)	6.9 (5.25)	5.5 (4.60)	6.2 (4.59)	2.2 (3.01)	4.2 (3.92)	2.1 (2.75)	3.5 (3.76)

Abbreviations: GMFI = geometric mean fold increase; GSD = geometric standard deviation; HI = hemagglutinin inhibition; n = number of subjects with nonmissing data; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.

Seroconversion rate based on HI Titres

Seroconversion (defined as becoming seropositive if seronegative at enrolment or at least a 4 fold increase in titres if seropositive at enrolment) rate is presented in Tables 9 and 10, below.

Adults:

- For the A(H3N2) strain and A(H1N1) strain, seroconversion rates were comparable between vaccination groups (A(H3N2) strain: QIV (51.3%); pooled TIV (58.6%); A(H1N1) strain: QIV (59.4%); pooled TIV (65.1%);
- For the B strain Victoria lineage, the seroconversion rates were comparable between QIV (70.2%) and $TIV_{(Vic)}$ (66.4%) groups. The seroconversion rate was lower in the $TIV_{(Yam)}$ group (51.4%) due to the limited cross-reactivity;
- For B strain Yamagata lineage, the seroconversion rates were comparable between QIV (59.2%) and $TIV_{(Yam)}$ (58.7%) groups. The seroconversion rate was lower in the $TIV_{(Vic)}$ group (40.9%) due to the limited cross-reactivity.

Elderly:

- For the A(H3N2) strain and A(H1N1) strain, the seroconversion rates were comparable between vaccination groups (A(H3N2) strain: QIV (39.3%); pooled TIV (44.0%); A(H1N1) strain: QIV, (50.3%); pooled TIV (57.4%);
- For the B strain Victoria lineage, the seroconversion rates were comparable between QIV (53.6%) and $TIV_{(Vic)}$ (55.6%) groups. The seroconversion rate was lower in the $TIV_{(Yam)}$ group 25.0% due to the limited cross-reactivity;
- For the B strain Yamagata lineage, the seroconversion rates were comparable between QIV (49.9%) and $TIV_{(Yam)}$ (46.2%) groups. The seroconversion rate was lower in the $TIV_{(Vic)}$ group (30.0%) due to the limited cross-reactivity.

Table 9: Seroconversion rates based on HI titres; FAS (Adults)

	A(H3N2)-Strain		A(H1N1)-Strain		B-Strain Victoria Lineage			B-Strain Yamagata Lineage		
Statistic	QIV (N = 768)	TIV* (N = 222)	QIV (N = 768)	TIV* (N = 222)	QIV (N = 768)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 112)	QIV (N = 768)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 112)
Postvaccination										
n	764	222	758	218	758	110	109	763	110	109
m (%)	392 (51.3)	130 (58.6)	450 (59.4)	142 (65.1)	532 (70.2)	73 (66.4)	56 (51.4)	452 (59.2)	45 (40.9)	64 (58.7)

Abbreviations: HI = hemagglutinin inhibition; n = number of subjects with nonmissing data; m = number of seroconverted subjects; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.

* HI titer data of the two trivalent formulations pooled for the two A-strains.

Table 10: Seroconversion rates based on HI titres; FAS (Elderly)

	A(H3N2)-Strain		A(H1N1)-Strain		B-Strain Victoria Lineage			B-Strain Yamagata Lineage		
Statistic	QIV (N = 765)	TIV* (N = 218)	QIV (N = 765)	TIV* (N = 218)	QIV (N = 765)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 108)	QIV (N = 765)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 108)
Postvaccination										
n	761	218	755	216	759	108	108	758	110	106
m (%)	299 (39.3)	96 (44.0)	380 (50.3)	124 (57.4)	407 (53.6)	60 (55.6)	27 (25.0)	378 (49.9)	33 (30.0)	49 (46.2)

Abbreviations: HI = hemagglutinin inhibition; n = number of subjects with nonmissing data; m = number of seroconverted subjects; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.

* HI titer data of the two trivalent formulations pooled for the two A-strains.

Geometric mean virus neutralisation titres

In both adult subjects and elderly subjects, the GMTs for VN increased in all vaccination groups from Day 1 (pre-vaccination) to the Day 22 visit (post-vaccination) for all 4 strains. The results for the PP subject sample were similar to the FAS.

Geometric mean virus neutralisation titres by fold increase

In both adult subjects and elderly subjects, the GMFI results for VN titres were in line with the HI titres, although the differences were less pronounced. The results for the PP subject sample were similar to the FA subject sample.

Seroconversion rate based on virus neutralisation titres

In both adult subjects and elderly subjects, the seroconversion rates based on VN titres were in line with the HI titres, although the differences were less pronounced. The seroconversion rate based on VN titres was repeated for the PP subject sample and results for the PP subject sample were similar to the FAS. The proportion of subjects with post-vaccination HI titres ≥ 40 for all 4 strains across all vaccination groups in adult subjects and elderly subjects, respectively are presented in Tables 11 and 12 (shown below). The proportion of subjects with post-vaccination HI titres ≥ 40 increased from Day 1 (pre-vaccination) to Day 22 (post-vaccination) for all 4 strains in both adult subjects and elderly subjects in all vaccination groups.

For the A (H3N2) strain in adult subjects, the post-vaccination HI titres ≥ 40 were reported in 97.8% in the QIV group compared to 95.9% in the pooled TIV group. In elderly subjects, the post-vaccination HI titres ≥ 40 were reported in 95.7% in the QIV group compared to 96.3% in the pooled TIV group.

For the A (H1N1) strain in adult subjects, the post-vaccination HI titres ≥ 40 were reported in 94.6% in the QIV group compared to 93.6% in the TIV group. In elderly subjects, the post-vaccination HI titres ≥ 40 were reported in 85.3% in the QIV group compared to 88.9% in the pooled TIV group.

For the B strain Victoria lineage in adult subjects, post-vaccination HI titres ≥ 40 were reported in 92.8% in the QIV group compared to 89.1% in the $TIV_{(Vic)}$ group and 79.1% in the $TIV_{(Yam)}$ group. In elderly subjects, the post-vaccination HI titres ≥ 40 were reported in 80.8% in the QIV group compared to 81.5% in the $TIV_{(Vic)}$ group and 63.0% in the $TIV_{(Yam)}$ group

For the B strain Yamagata lineage in adult subjects, post-vaccination HI titres ≥ 40 were reported in 91.6% in the QIV group compared to 78.2% in the $TIV_{(Vic)}$ group and 90.0% in the $TIV_{(Yam)}$ group. In elderly subjects, the post-vaccination HI titres ≥ 40 were reported in 73.3% in the QIV group compared to 51.8% in the $TIV_{(Vic)}$ group and 73.6% in the $TIV_{(Yam)}$ group.

Table 11: Proportion of subjects with post-vaccination HI titres ≥ 40; FAS (adults)

	Statistic	A(H3N2)-Strain		A(H1N1)-Strain		B-Strain Victoria Lineage			B-Strain Yamagata Lineage		
HI Titer ≥ 40		QIV (N = 768)	TIV* (N = 222)	QIV (N = 768)	TIV* (N = 222)	QIV (N = 768)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 112)	QIV (N = 768)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 112)
Postvaccination (Day 22)	n	766	222	759	220	764	110	110	765	110	110
	m (%)	749 (97.8)	213 (95.9)	718 (94.6)	206 (93.6)	709 (92.8)	98 (89.1)	87 (79.1)	701 (91.6)	86 (78.2)	99 (90.0)

Abbreviations: HI = hemagglutinin inhibition; m = number of subjects in each category; n = number of subjects with available data; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.

* HI titer data of the two trivalent formulations were pooled for the two A-strains.

Table 12: Proportion of subjects with post-vaccination HI titres ≥ 40; FAS (elderly)

	Statistic	A(H3N2)-Strain		A(H1N1)-Strain		B-Strain Victoria Lineage			B-Strain Yamagata Lineage		
HI Titer ≥ 40		QIV (N = 765)	TIV* (N = 218)	QIV (N = 765)	TIV* (N = 218)	QIV (N = 765)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 108)	QIV (N = 765)	$TIV_{(Vic)}$ (N = 110)	$TIV_{(Yam)}$ (N = 108)
Postvaccination (Day 22)	n	763	218	757	217	762	108	108	760	110	106
	m (%)	730 (95.7)	210 (96.3)	646 (85.3)	193 (88.9)	616 (80.8)	88 (81.5)	68 (63.0)	557 (73.3)	57 (51.8)	78 (73.6)

Abbreviations: HI = hemagglutinin inhibition; m = number of subjects in each category; n = number of subjects with available data; QIV = quadrivalent influenza vaccine; TIV = trivalent influenza vaccine; Vic = Victoria; Yam = Yamagata.

* HI titer data of the two trivalent formulations were pooled for the two A-strains.

7.2.1.14. Evaluator commentary

The study design was appropriate with adequate power for the primary and key secondary endpoints. Several endpoints exploring T cell immune responses in a subset are exploratory and not discussed above. The study demonstrated in all age groups studied (adults and the elderly) first that the post-vaccination geometric mean HI titres of all influenza strains in QIV were non-inferior to the shared strains contained in the TIV formulations and second, there were superior immune responses (as measured by post-vaccination geometric mean HI antibody titres) for each of the B strain lineages in the QIV when compared to the TIVs with the alternate B strain lineage. Geometric mean fold increases based on HI titres was > 6.3 in adult subjects and > 4.2 in elderly subjects in the QIV group for all 4 strains. Seroconversion based on HI titres was found in > 51.0% of the adult subjects and > 39.0% of the elderly subjects in the QIV group for all 4 strains. More than 91.0% of the adult subjects and > 73.0% of the elderly subjects in the QIV group had post-vaccination HI titres ≥ 40 for all 4 strains.

7.3. Analyses performed across trials: pooled and meta analyses

Post-vaccination GMTs found in the QIV and TIV formulations in Study INFQ3001 against the TIV formulation in the 16 supportive studies of Influvac, boxplots of the post-vaccination geometric mean HI titres per strain are displayed in Figures 3 and 4 (shown below) for the adults and elderly adults, respectively. In summary, the post-vaccination GMTs of the QIV and TIV formulations used in Study INFQ3001 are within the expected range of the pooled post-vaccination GMTs of the 16 TIV studies in the clinical study database of Influvac.

7.3.1. Adults

7.3.1.1. Comparison of QIV in INFQ3001 against TIV supportive studies

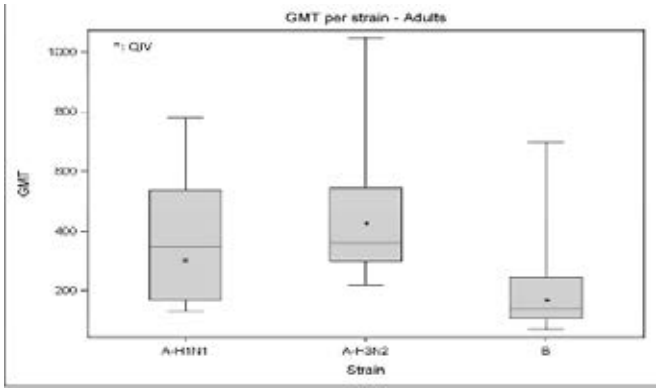
For the H3N2 strain, the post-vaccination GMT for QIV in Study INFQ3001 was 442.4, which is within the interquartile range of the pooled TIV studies (300.9 to 545.0). For the H1N1 strain, the post-vaccination GMT for QIV was 272.2, which also fell within the interquartile range of the pooled TIV studies (170.4 to 538.2).

For the B strain Victoria lineage and Yamagata lineage, the post-vaccination GMT for QIV was 214.0 and 162.5, respectively, which is within the interquartile range of the pooled TIV studies (108.8 to 246.9).

7.3.1.2. Comparison TIV in INFQ3001 against TIV supportive studies

For the H3N2 strain, the post-vaccination GMT for TIV in Study INFQ3001 was 473.5, which is within the interquartile range of the pooled TIV studies (300.9 to 545.0). For the H1N1 strain, the post-vaccination GMT for TIV was 310.1, which also fell within the interquartile range of the pooled TIV studies (170.4 to 538.2). For the B strain Victoria lineage and Yamagata lineage, the GMT for TIV was 184.7 and 128.7, respectively, which is within the interquartile range of the pooled TIV studies (108.8 to 246.9).

Figure 3: Geometric mean HI titres; Adults, Clinical Study Database for Influvac



7.3.2. Elderly adults

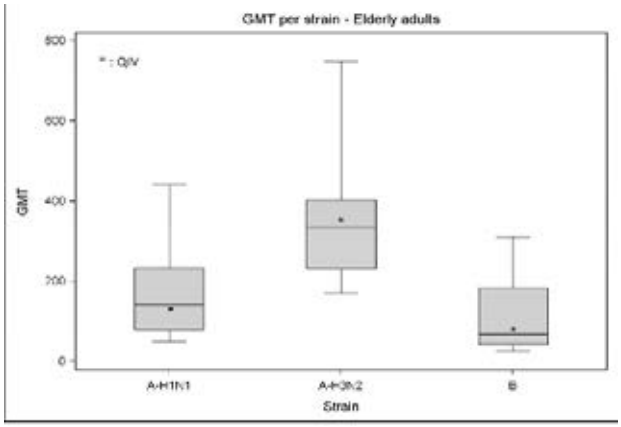
7.3.2.1. Comparison QIV in INFQ3001 against TIV supportive studies

For the H3N2 strain, the post-vaccination GMT for QIV in Study INFQ3001 was 348.5, which is within the interquartile range of the pooled TIV studies (231.5 to 402.5). For the H1N1 strain, the post-vaccination GMT for QIV was 127.2, which also fell within the interquartile range of the pooled TIV studies (80.0 to 233.6). For the B strain Victoria lineage and Yamagata lineage, the post-vaccination GMT for QIV was 109.4 and 63.7, respectively, which is within the interquartile range of the pooled TIV studies (42.6 to 182.9).

7.3.2.2. Comparison TIV in INFQ3001 against TIV supportive studies

For the H3N2 strain, the post-vaccination GMT for TIV in Study INFQ3001 was 357.4, which is within the interquartile range of the pooled TIV studies (231.5 to 402.5). For the H1N1 strain, the post-vaccination GMT for TIV was 157.7, which also fell within the interquartile range of the pooled TIV studies (80.0 to 233.6). For the B strain Victoria lineage and Yamagata lineage, the post-vaccination GMT for TIV was 106.6 and 57.4, respectively, which is within the interquartile range of the pooled TIV studies (42.6 to 182.9).

Figure 4: Geometric mean HI titres; Elderly adults, Clinical Study Database for Influvac



7.4. Evaluator's conclusions on clinical efficacy

Study INFQ3001 conducted entirely within the European Union, demonstrates the immunogenicity of Influvac Tetra in adults aged 18 to 60 years and the elderly aged ≥ 61 years against all 4 strains of influenza virus contained within the vaccine. Standard methodology to demonstrate immunogenicity was utilised. Importantly, the added B strain provides superior immunogenicity without affecting the antibody response to the other strains and there is no safety cost (discussed in Section 8, below). Seroprotection rates for all 4 strains in the QIV were

higher in adults compared to the elderly, but nevertheless high in both groups. Lower seroprotection in the elderly is a universal finding in immunogenicity studies for influenza vaccines (that is, not a unique finding for this vaccine) and the reviewer has no concerns about this finding in the pivotal study and the pooled analyses.

8. Clinical safety

There is one key study, Study INFQ3001, described in Section 7 (above) that provided evaluable safety data for the QIV. The study aimed to demonstrate that the safety and reactogenicity of QIV is comparable to those of TIVs. The extensive safety data collected for Influvac is considered supportive of QIV development, as the antigens of the influenza strains in QIV are similar to those from TIV formulations over the years (apart from the fact that QIV now combines 2 B strain lineages in one formulation). Influvac has shown a favourable safety profile in both healthy and at-risk populations, and no unexpected safety signals that would warrant specific additional risk minimisation activities have been observed to date. Therefore, standard safety outcome parameters for influenza vaccine studies were used, that is, solicited local and systemic reactions (reactogenicity), overall inconvenience, and other unsolicited AEs. For the 6 month safety follow up, only new SAEs and NCIs were reported.

Safety reporting parameters are defined as follows:

- *AE:* An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product. *The post therapy AE collection period is defined as the period up to Visit 2 (until Day 22 after study vaccination).*
- Solicited AEs and Unsolicited AEs (as defined in Section 7) graded for severity as follows:
  - Mild: Symptoms are easily tolerated and do not interfere with normal, everyday activities;
  - Moderate: Discomfort enough to cause some interference with normal, everyday activities;
  - Severe: Symptoms that prevent normal, everyday activities.
- New Chronic illnesses (NCI): Collected from informed consent to study end, that is, Phone Contact 2 (Day 183).
- SAE: Untoward medical occurrence that results in death; is life-threatening; requires in patient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is an important medical event; is the suspected transmission of an infectious agent via a medicinal product. Collected from signing informed consent to study end, that is, Phone contact 2 (Day 183).
- Severity Of AEs: Assessed by the investigator as follows:
  - Mild: Usually transient and do not interfere with the subject's daily activities;
  - Moderate: Low level of inconvenience or concern to the subject and may interfere with daily activities;
  - Severe: Interrupt the subject's usual daily activity.
- Causality of AEs: Assessed by investigator as unrelated, unlikely, possible or probable.

8.1. Studies providing evaluable safety data

Study INFQ3001, described in Section 7 (above) collected safety data as a secondary outcome.

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

No studies.

8.1.1.1. Evaluator commentary

Study INFQ3001 was deemed a large enough study to assess the safety of the QIV compared to the TIVs in the study. The reason why this relatively small study is adequate is that QIV is not considered a completely new vaccine which would necessitate higher number of vaccines in order to characterise safety. The extensive safety data collected with the TIV, Influvac, is considered supportive for the QIV development, since the production process for QIV and Influvac are identical and importantly both B strain lineages have been alternatingly present in the TIV formulation over many years, without safety concerns.

8.2. Patient exposure

1535 adults received a single dose of the QIV (See Section 7, above). Of the 990 vaccinated adult subjects, 768 received a single vaccination of QIV, and 222 subjects received a single vaccination of TIV on Day 1. Of the 986 vaccinated elderly adults, 767 received a single vaccination of QIV, and 219 subjects received a single vaccination of TIV on Day 1.

8.3. Adverse events

Integrated analyses performed on the safety data of the current thiomersal free formulation of the TIV, Influvac, was restricted to healthy adults (18 to 60 years of age) and elderly adults (≥ 61 years of age) who received a single vaccination of the standard trivalent dose, that is, 15 µg of an A (H1N1) strain, 15 µg of an A (H3N2) strain and 15 µg of a B strain, and for whom safety data are available. The list of solicited local and systemic reactions differs between studies. Some reactions were solicited in almost all studies; others were solicited in only few studies. In most of the studies, 9 local reactions (redness, swelling, itching, warmth, pain, tenderness, impairment of arm movement, induration and ecchymosis) and 6 systemic reactions (fever, increased sweating, headache, malaise, insomnia or fatigue, and shivering) were recorded daily by the subjects participating in the studies. Insomnia was included for all studies until 2007 and was replaced by fatigue from 2008 onwards. In the study performed in China (Study S201.3.121) rash was added to the local reactions and allergic reactions, cough, myalgia, malaise/fatigue, nausea/vomiting and diarrhoea were added to the systemic reactions as per Chinese regulatory requirements. In the 2 studies (Studies S203.2.009 and S203.3.013) where Influvac was used as a comparator, myalgia and arthralgia were added to the systemic reactions.

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

8.3.1.1. Integrated safety analyses (Clinical Study Database Influvac)

AEs were evaluated in 1473 adults and 1744 elderly adults up to Day 22 post-vaccination. During the first 3 weeks after vaccination, TEAEs were reported in 9.8% of the adults and 7.5% of the elderly adults. None of the subjects died up to Day 22 of the supportive TIV studies. The % of subjects with ≥ 1 TEAE considered to have a reasonable possibility for a causal relationship with the study vaccine was 1.9% and 1.3%, respectively. TEAEs were reported most commonly in the 'Infections and infestations', 3.1% of the adult subjects 1.4% of the elderly subjects. Most frequently reported TEAEs were headache (1.4% of the adults and 0.3% of the elderly) and oropharyngeal pain (1.4% and 0.4%, respectively), followed by nasal congestion (1.0% and 0.1%, respectively), nasopharyngitis and URTI (both 0.7% and 0.2%, respectively). All other

TEAEs reported by 0.5% of the subjects or less. TESAEs were reported by 3 adults (0.2%; 3 events) and 7 (0.4%; 7 events) elderly adults.

8.3.1.1. Pivotal and/or main efficacy studies (Study INFQ3001)

Adults

4.5% of subjects reported ≥ 1 TEAE up to the Day 22 visit; 4.8% subjects in the QIV group and 3.6% subjects in the TIV group. No subject died or discontinued the study up to the Day 22 visit due to TEAEs. A total of 0.5% and 0.9% of the subjects in the QIV and TIV groups, respectively, had ≥ 1 TEAE considered to have a reasonable possibility for a causal relationship with the study vaccine. 3 subjects (0.3%) in the QIV group reported TEAEs that were severe. However, the proportion of subjects with TEAEs was similar across vaccination groups. TEAEs were reported most frequently in the SOC of 'Infections and infestations' (14 adult subjects (1.8%) in the QIV group and 2 adult subjects (0.9%) in the TIV group). No TEAE was reported in > 2 adult subjects for any PT in either vaccination group. No flagging occurred (= 1.0 not included in the CI for the rate ratio between the QIV and the TIV group). 2 adult subjects from the QIV group experienced one TESAE each (cartilage injury and hand fracture) up to the Day 22 visit.

Of the TEAEs, the majority were mild.

QIV group: TEAEs assessed as moderate in severity: animal bite, arthropod bite, wound, gastritis, intervertebral disc protrusion, arthralgia, myalgia, dizziness, and allergic conjunctivitis (reported in 1 subject (0.1%) each). Arthralgia and myalgia were systemic reactions that occurred after Day 7 and hence were reported as TEAEs. TEAEs assessed as severe: hand fracture, cartilage injury, and gastritis (reported in 1 subject (0.1%) each).

TIV group: TEAEs assessed as moderate in severity: cluster headache and ILI (reported in 1 subject (0.5%) each). None of TEAEs assessed as severe by the Investigator in the TIV group.

Elderly adults

Overall, 3.5% of subjects reported ≥ 1 TEAE up to the Day 22 visit; 3.8% subjects in the QIV group and 2.7% subjects in the TIV group. No subject died or discontinued up to the Day 22 visit due to TEAEs. 5 subjects (0.5%) reported 6 TESAEs. A total of 0.8% and 0.9% of subjects in the QIV and TIV groups, respectively, had ≥ one TEAE that was considered to have a reasonable possibility for a causal relationship with the study vaccine. Overall, 4 subjects (0.4%) reported 4 TEAEs that were severe in severity. However, the proportion of subjects with TEAEs was similar across vaccination groups. TEAEs were reported most commonly in the 'Infections and infestations' SOC (11 subjects (1.4%) in the QIV group and 2 elderly adults (0.9%) in the TIV group). No TEAE was reported in > 2 elderly adults for any PT in either vaccination group. No flagging occurred in this age group.

5 elderly adults experienced a total of 6 TESAEs up to the Day 22 visit. Of these, 4 TESAEs (abdominal wall abscess, atrial fibrillation, foot fracture, and rotator cuff syndrome) were reported in 1 elderly adult each from the QIV group and 2 TESAEs (sub-acute endocarditis and arterial embolism) were reported in 1 elderly adult from the TIV group. Of the TEAEs that were reported in elderly adults, the majority were mild in severity.

Moderate TEAEs

- QIV group: URTI, cystitis, bronchitis, back pain, dyspnoea, chronic pancreatitis, somnolence, atrial fibrillation, contusion, and hepatic cirrhosis (reported in 1 subject (0.1%) each).
- TIV group: sub-acute endocarditis, spinal osteoarthritis, and aortic valve incompetence (reported in 1 subject (0.5%) each).

Severe TEAEs

- QIV group: abdominal wall abscess, rotator cuff syndrome, and foot fracture (reported in 1 subject (0.1%) each).

· TIV group: arterial embolism (reported in 1 subject (0.5%)).

8.3.2. Treatment related adverse events (adverse drug reactions)

8.3.2.1. Integrated safety analyses (Clinical Study Database Influvac)

Treatment-related TESAEs were reported by 1.9% adults and 1.3% elderly adults. The most frequently reported TRAEs are nasal congestion (0.7% of the adults and 0.1% of the elderly) and oropharyngeal pain (0.6% and 0.1%, respectively), followed by cough (0.3% and 0.2%, respectively), nasopharyngitis (0.3% and 0.1%, respectively), pain and headache (both 0.2% in adults only). All other TRAEs were reported by 0.1% of the subjects.

8.3.2.2. Pivotal and/or main efficacy studies (Study INFQ3001)

Adults: Proportion with vaccine-related TEAEs was 0.6% across vaccination groups; 4 subjects (0.5%) in the QIV group and 2 subjects (0.9%) in the TIV group. The PT asthenia was the only TEAE reported in > 1 subject (2 subjects (0.3%) in the QIV group.

Elderly adults: Proportion with vaccine-related TEAEs was 0.8% across the vaccination groups; 6 subjects (0.8%) in the QIV group and 2 subjects (0.9%) in the TIV group. None of the vaccine-related TEAEs were reported in > 1 subject for any PT in either vaccination group.

Reactogenicity within 7 Days after vaccination: Local reactions

Adults: Rates were generally low (< 10%) except vaccination site pain in 24.9% in the QIV group and 18.5% in the TIV group. One subject each in the QIV group had severe swelling and vaccination site pain. Except for vaccination site pain, reporting rates of all other local reactions were slightly lower in the QIV group than in the TIV group. None of the differences reached statistical significance and were not flagged as a potential safety issue.

Elderly: The percentage of elderly adults with local reactions within 7 days after vaccination was low (< 5%) except for vaccination site pain that occurred in 7.6% in the QIV group and 5.9% in the TIV group. One subject in the QIV group had severe induration, 2 subjects in the TIV group had severe swelling, and 1 subject in the TIV group had severe induration. Although reporting rates were slightly higher in the QIV group in elderly adults, none of the differences reached statistical significance and were not flagged as a potential safety issue.

For both adult and elderly adults, most of the local reactions were mild or moderate in severity. Overall, all local reaction symptoms lasted for 1 to 3 days for the majority of subjects in both vaccination groups.

Reactogenicity within 7 days after vaccination: Systemic reactions

Adults: Headache and fatigue/tiredness were the most frequent systemic reactions within 7 days after vaccination in both vaccination groups. Headache reported by 12.4% of subjects in the QIV group and 13.1% in the TIV group. Fatigue/tiredness reported by 11.9% and 12.6% of subjects in the QIV and TIV groups, respectively. Most systemic reactions were mild or moderate. Severe reactions reported in ≤0.3% in the QIV group and ≤0.9% in the TIV group. Duration was 1-3 days for the majority of subjects in both vaccination groups. Reporting rates and relative risks of systemic reactions were comparable between the QIV group and the TIV group.

Elderly: Headache and fatigue/tiredness were the most frequent systemic reactions within 7 days after vaccination in both vaccination groups. Headache reported by 8.1% in the QIV group and 7.3% in the TIV group. Fatigue/tiredness reported by 10.6% and 6.8% of subjects in the QIV and TIV groups, respectively. Most systemic reactions were mild or moderate. Severe reactions reported in ≤ 0.7% in the QIV group and ≤ 0.5% in the TIV group. Duration was 1 to 3 days for the majority of subjects in both vaccination groups. Differences in rates between QIV and TIV were relatively small, although only one reaction (arthralgia/joint pain, 5.8% (QIV) versus 2.3%

(TIV)) reached statistical significance (see Table 13, below), thus was flagged as having a potentially higher reporting rate for elderly subjects in the QIV group.

Table 13: Study INFQ3001 systemic reactions, reporting rates and relative risks; safety subject sample, elderly population

	Arthralgia/joint pain		Malaise		Sweating		Shivering	
Statistic	QIV (N=767)	TIV* (N=219)	QIV (N=767)	TIV* (N=219)	QIV (N=767)	TIV* (N=219)	QIV (N=767)	TIV* (N=219)
n	762	219	762	219	762	219	762	219
m (%)	44 (5.8)	5 (2.3)	49 (6.4)	10 (4.6)	45 (5.9)	9 (4.1)	36 (4.7)	6 (2.7)
Crude RR (95 % CI)	2.5 (1.0,6.3)		1.4 (0.7,2.7)		1.4 (0.7,2.9)		1.7 (0.7,4.0)	
Adjusted RR** (95 % CI)	2.9 (1.1,7.6)		1.6 (0.8,3.0)		1.6 (0.8,3.3)		2.1 (0.8,5.0)	

Note: n = Number of subjects with available data, m = Number of subjects with systemic reactions.
Note: *Reactogenicity data of the two trivalent formulations pooled; RR: Relative Risk QIV vs TIV.
Note: Two sided 95 % CI is obtained based on Mantel Haenszel method.
Note: **Adjusted for country and center.
Note: NE = Not Evaluable.
Source: RGT005.SAS, PPD. Run 25MAY2016 11:39

Clinical study database influvac

Local Reactions: Most frequently reported reaction was vaccination site pain (13.4% of the adults and 3.8% of the elderly). All other local reactions were reported by 3.2 to 6.1% of the adults and by 1.7-3.0% of the elderly adults. Most local reactions were mild, resolving within 3 days. Elderly adults reported fewer local reactions than the adults.

Systemic Reactions: Most frequently reported systemic reactions were fatigue (14.4% of the adults and 9.1% of the elderly), and headache (12.0% and 7.4%, respectively). All other systemic reactions reported by 0.5-8.9% of the adults and by 0.5% to 4.8% of the elderly. Most systemic reactions were mild, resolving within 3 days. Elderly adults reported fewer systemic reactions than the adults.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Deaths

No deaths reported up to Day 22 post-vaccination in Study INFQ3001 or in the 16 supportive clinical studies for TIV.

Deaths post day 22 (Study INFQ3001)

Of the reported TESAEs (severe cardiac disorder), outcome was fatal (unrelated to study vaccine) for 1 adult subject in the QIV group. Of the reported TESAEs, outcome was fatal for 4 elderly adults in the QIV group: oesophageal carcinoma, pancreatic carcinoma, hepatic failure, and congestive cardiac failure. None of the TESAEs were considered related to study vaccine.

8.3.3.2. SAEs (Study INFQ3001)

No pregnancies up to the Day 22 visit; 5 pregnancies between Day 22 to Month-6 post-vaccination. 2 subjects had spontaneous abortions; one subject had an elective termination; 2 subjects had full term pregnancies with normal outcomes. These events judged as unrelated to study vaccination.

SAEs up to the day 22 visit

Adults: 2 in the QIV group experienced one TESAE each (cartilage injury and hand fracture) up to the Day 22 visit.

Elderly: 5 experienced a total of 6 TESAEs up to the Day 22 visit. Of these, 4 TESAEs, that is, abdominal wall abscess, atrial fibrillation, foot fracture, and rotator cuff syndrome, were reported in 1 subject each from the QIV group and 2 TESAE (sub-acute endocarditis and arterial embolism) were reported in 1 subject from the TIV group. Atrial fibrillation and subacute

endocarditis were of moderate intensity, all others were severe. None considered study vaccine related.

SAE from the day 22 visit to study end

Adults: Similar across the vaccination groups (1.3% and 1.8% in the QIV and TIV groups, respectively). No TESAEs reported in > 1 subject for any PT in either vaccination group, except hypertension that was reported in 2 subjects (0.3%) in the QIV group. All TESAEs considered not related or unlikely related to the study vaccine.

Elderly: Similar across the vaccination groups (3.9% and 4.1% in the QIV and TIV groups, respectively). No TESAEs reported in > 1 subject for any PT in either vaccination group, except cerebrovascular accident reported in 2 subjects (0.3%) in the QIV group. All TESAEs considered not related to the study vaccine*.*

NCI (collected day 22 visit up to the Month-6 telephone call).

Adults: Similar across the groups (1.3% and 1.4% in the QIV and TIV groups, respectively). No NCIs reported in > 1 subject for any PT in either vaccination group, except spinal osteoarthritis reported in 2 subjects (0.3%) in the QIV group.

Elderly: Similar across the groups (4.0% and 2.3% in the QIV and TIV groups, respectively). No NCIs reported in > 1 subject for any PT in either vaccination group, except for the following illnesses in the QIV group: cataract reported in 5 subjects (0.7%); osteoarthritis reported in 3 subjects (0.4%); and gastroenteritis, atrial fibrillation, and hypothyroidism each reported in 2 subjects (0.3%). None of the NCIs considered related to the study vaccine.

8.3.3.3. Clinical study database influvac

Pregnancy: 2 subjects became pregnant during the study: normal pregnancy outcome with live births. One subject vaccinated in the supportive TIV study S203.3.013 (conducted in Australia) became pregnant between the Day 22 visit and Month 6 post-vaccination. She had a full term pregnancy with normal outcome.

Unsolicited AEs: in those in whom these could be evaluated, 3 adults and 7 elderly adults reported 10 TESAEs in total in the study period up to 3 weeks after vaccination. All the reported TESAEs were considered not related to study vaccine.

Adults: 3 subjects experienced one TESAE each, that is, type I diabetes mellitus, shoulder surgery, acute appendicitis, considered to be of mild, moderate and severe intensity, respectively.

Elderly: 7 experienced the following TESAEs, that is, pancreatic neoplasm, coronary artery disease, transient ischemic attack, adenocarcinoma of the prostate and urinary retention secondary to benign prostatic hyperplasia, radiculitis secondary to osteoarthritis, chest pain and confusion. Radiculitis and chest pain were considered to be moderate, all other TESAEs were severe.

8.3.3.4. Extended safety (SAE and NCI) follow-up (Day 22 up to 6 months post-vaccination)

This was performed in 2 studies (Studies S203.2.009 and S203.3.013).

Deaths: Outcome fatal (congestive cardiac failure in 1 subject and metastatic pancreatic carcinoma and peritonitis in 1 subject) for 2 elderly adults during the period from Day 22 up to 6 months post-vaccination. None considered vaccine-related.

Other SAEs:

- Study S203.2009 (first year): The proportion of elderly adults reported with ≥ 1 TESAE was 3.9%. The most commonly reported TESAE was angina pectoris (2 subjects). No other TESAEs were reported in more than one subject. None considered vaccine-related.

- Study S203.2009 (second year): The proportion of subjects reported with at least one TESAE from the Year 2 Day 22 Visit up to the Year 2 Month 6-telephone call of the study was 3.5%. No TESAEs were reported in more than one subject. None considered vaccine related.

NCI:

- Study S203.2009 (first year): 9.2% subjects with at least one NCI reported. No NCI reported in ≥ 5%. The most common NCI was osteoarthritis (5 (2.4%) subjects). None considered vaccine-related.
- Study S203.2009 (second year): 7.0% subjects with ≥ 1 NCI reported. No NCI reported in ≥ 2%. Most common NCI was osteoarthritis (2 (1.4%) subjects). None considered vaccine-related.

8.3.4. Discontinuations due to adverse events

8.3.4.1. Integrated safety analyses

Overall, 0.7% prematurely withdrew from the studies, 10 (0.7%) adults and 13 (0.7%) elderly adults. Reasons reported: lost to follow-up (7 adults and 6 elderly adults), and AE (6 elderly adults with SAEs), withdrawal of consent (1 adult and 1 elderly adult), and lack of time (due to personal reasons, 2 adult subjects).

8.3.4.2. Pivotal and/or main efficacy studies (Study INFQ3001)

Overall, 11 subjects (0.6%) prematurely withdrew from the study. The number of premature withdrawals was 8 subjects (0.5%) assigned to QIV, 1 subject (0.5%) to $TIV_{(Vic)}$ and 2 subjects (0.9%) to $TIV_{(Yam)}$. Reasons reported: withdrawal of consent (4 subjects), AE (3 subjects with fatal TEAEs, lost to follow-up (3 subjects) and administrative (1 subject). No subject reported a TEAE up to the Day 22 visit leading to study termination.

8.4. Evaluation of issues in Study INFQ3001 with possible regulatory impact

8.4.1. Liver function and liver toxicity

Not assessed.

8.4.2. Renal function and renal toxicity

Not assessed.

8.4.3. Other clinical chemistry

Not assessed.

8.4.4. Haematology and haematological toxicity

Not assessed.

8.4.5. Electrocardiograph findings and cardiovascular safety

Not applicable, not assessed.

8.4.6. Vital signs and clinical examination findings

None revealed.

8.4.7. Immunogenicity and immunological events

None revealed in Study INFQ3001. According to the current EU RMP; Version 3.0, DLP 29 February 2016, hypersensitivity is characterised as the only important identified risk for the seasonal influenza vaccine Influvac.

8.4.8. Serious skin reactions

None seen.

8.5. Other safety issues

8.5.1. Safety in special populations

Not assessed.

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

Not assessed.

8.6. Post marketing experience

Not applicable, this is a new drug application. However, PSURs numbers 17 (1 May 2011 to 30 April 2012) to number 24 (1 September 2015 to 15 March 2016) inclusive for the TIV were submitted with this application. The quadrivalent influenza vaccine described in the sponsor's Summary of Clinical Safety is currently not marketed, therefore only post-marketing safety data from the marketed thiomersal-free TIV was presented and is summarised as part of the integrated safety analysis data. Based on market data, > 350 million doses of the current thiomersal free formulation of the subunit influenza vaccine have been administered between 2004 and 30 April 2016. Considering the large number of patients vaccinated with influenza vaccine and the low number of AEs reported, the vaccine is regarded as safe and well tolerated.

8.7. Evaluator's overall conclusions on clinical safety

In line with the scientific advice obtained from a EU national authority, the exposure of around 1,500 adult subjects to QIV is deemed sufficient to demonstrate the safety of QIV. This exposure is lower than specified in the Note for Guidance on the 'Clinical Evaluation of New Vaccines' (EMEA/CHMP/VWP/164653/2005), which recommends at least 3,000 subjects. However, QIV is not considered a completely new vaccine which would necessitate higher number of vaccinees in order to characterise safety. The extensive safety data collected with the related TIV, Influvac, is considered supportive for the QIV development, since the production process for QIV and Influvac are identical (aside from QIV containing both B strain lineages). Moreover, both B strain lineages have been alternatingly present in the TIV formulation over the years.

In Study INFQ3001, the safety profile of QIV in adults and elderly adults is generally similar to that observed for the comparator TIV vaccines within the study and similar to the integrated safety analyses derived from the 16 supporting immunogenicity studies. There was no concerning safety signal revealed with respect to solicited local and systemic reactogenicity, TRAEs or SAEs in either the adult or elderly populations studied. The reviewer notes the slightly increased recorded incidence of arthralgia/joint pain post vaccination in the elderly population receiving the QIV vaccine, but despite this, the rates were still low. Overall, the clinical evaluator thinks that QIV has a clinically acceptable safety and tolerability profile in adults aged ≥ 18 years at least in the relatively small number of patients enrolled in this study exposed to single dose QIV. As Influvac has been marketed for several decades, no additional risks, which might be based on known class effects or known pharmacologic properties, are expected to occur.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Table 14: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
· Influvac Tetra in the proposed usage provides better coverage of the influenza B strains than the TIV; · QIV was immunogenic against all 4 strains it contains in both the adult and elderly populations; · the safety profile of this QIV is similar to trivalent inactivated influenza vaccines in general, and to the specific TIV comparators used in the pivotal efficacy study; · the inclusion of both B strains will overcome the problem of poor predictions of which B strain is likely to circulate, this has been problematic over the last few years and has led to misalignment of the B strain in the recommended TIV with the circulating B strain.	· Paucity of data for the QIV in younger adults; · paucity of data for the QIV in adults and the elderly of Black or Asian ethnicity; · no data on immunogenicity or safety of repeat dosing with the QIV; · no data on immunogenicity or safety of repeat dosing with a QIV manufactured by a different company; · other QIV flu vaccines are available, so this QIV will not fill a 'gap in the market'.

9.2. First round assessment of risks

The risks of Influvac Tetra in the proposed usage are shown in Table 15, below.

Table 15: First round assessment of risks

Risks	Strengths and Uncertainties
· There is no data on the immunogenicity and safety profile in immunocompromised patients as such patients were specifically excluded from participation; · Hardly any data for the QIV in subjects of Asian ethnicity; · nil data for the QIV in Australian indigenous ethnicity; this is relevant to the Australian population; · no data presented for the safety of QIV in lactating women, yet the product information states Influvac Tetra can be used during lactation.	· (Related to first bullet point, left) Flagged in the PI; as detailed in the RMP, '*Other routine measures including monitoring and reporting of post-marketing safety data and signal detection in the immunocompromised*'. · (Related to bullet points 2 to 4 left), no indication from the TIV data that immunogenicity and safety of the QIV will be any different in these different ethnicities or in lactating women. Although there is no data on immunogenicity and safety of this QIV in pregnancy or lactation, use in pregnant and breast-feeding women is not an identified Safety Concern in the EU-RMP.

Risks	Strengths and Uncertainties
	There is a clear plan for the collection of safety data in pregnancy and lactation, which will be reported as a summary data in the PSURs.

9.3. First round assessment of benefit-risk balance

The first round assessment of benefit-risk balance is favourable.

10. First round recommendation regarding authorisation

The clinical evaluator recommends authorisation.

11. Clinical questions

The clinical evaluator had no questions for the sponsor.

12. Second round benefit-risk assessment

Following the satisfactory assessment of the Influvac Tetra in the first round, the submission proceeded to Delegate's overview. See the associated AusPAR for further details.

13. References

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