EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 October 2018
EMA/814746/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Flucelvax Tetra

Common name: Influenza vaccine (surface antigen inactivated prepared in cell cultures)

Procedure No. EMEA/H/C/004814/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CQA	Clinical quality assurance
CPP	Critical process parameters
CSR	Clinical study report
CT	Clinical trial
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
FCC	Flu cell culture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric mean titer
GMR	Geometric mean ratio
HA	Hemagglutinin
HI	Hemagglutination inhibition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILI	Influenza-like illness
MAA	Marketing Authorization Application
MDCK	Madin Darby Canine Kidney
NA	Neuraminidase
NVD	Novartis Vaccines and Diagnostics
NOCD	New onset of chronic disease
PPS	Per protocol set
QIV	Quadrivalent influenza vaccine
QIVc	Quadrivalent influenza virus vaccine (surface antigen, inactivated, cell-based) or Flucelvax Tetra
SA	Scientific advice

SAE Serious adverse event

SCR Seroconversion rate

SD Standard deviation

SOC System organ class

TIV Trivalent influenza vaccine

TIVc Cell-based, trivalent influenza vaccine

TIV1c TIVc formulation containing all 3 WHO recommended strains for trivalent influenza virus vaccine composition (including B/Massachusetts)

TIV2c TIVc formulation containing both WHO recommended A strains for trivalent influenza virus vaccine composition and the influenza B/Brisbane strain from the alternate Victoria lineage

TIVe Egg-derived, trivalent, inactivated, influenza vaccine

TIVeA Egg-derived trivalent influenza vaccine (Agrippal)

TIVeF Egg-derived trivalent influenza vaccine (Fluvirin)

UK United Kingdom

US United States of America

WHO World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Seqirus UK Limited submitted on 23 October 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Flucelvax Tetra, through the centralised procedure under Article 28 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 April 2017.

The applicant applied for the following indication:

Prophylaxis of influenza. Flucelvax Tetra should be used in accordance with official guidance. Flucelvax Tetra is indicated in adults and children from 4 years of age.

The applicant has changed to Seqirus Netherlands B.V. during the procedure at Day 181.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0341/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0341/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	date	Area
EMEA/H/SA/2628/2/2013/PED/III	23 January 2014	Quality, non-clinical and clinical
EMEA/H/SA/2628/FU/1/2016/PED/II	23 June 2016	Clinical
EMEA/H/SA/2628/1/FU/1/2017/III	23 February 2017	Quality, non-clinical and clinical

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sol Ruiz Co-Rapporteur: Joseph Emmerich

The application was received by the EMA on	31 October 2017
The procedure started on	23 November 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 March 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 May 2018
The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GMP inspection of the manufacturing site Seqirus Inc., 475 Green Oaks Parkway Holly Springs NC 27540 UNITED STATES was performed between 27 June and 3 July 2018. The outcome of the inspection carried out was issued on	07 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	03 July 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 July 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 July 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	06 September 2018
Vaccine Working Party experts (VWP) were convened to address questions raised by the CHMP on The CHMP considered the views of the Vaccine Working Party as presented in the minutes of this meeting.	7 September 2018

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Flucelvax Tetra on	18 October 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease

Influenza is a highly infectious disease that occurs in epidemics throughout the winter months. The disease is caused by transmission of respiratory droplets containing the influenza virus particles. Influenza illness is characterized by the abrupt onset of respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis. The disease presents as a non-specific systemic illness which may be complicated by a range of viral or bacterial infections. Clinical manifestations are generally consistent across adult and paediatric populations, however variability in clinical presentation may occur within or between adult, older adult or paediatric age groups, and some manifestations may be age-specific, such as irritability in young children. Fever tends to be less frequent and less pronounced in older adults compared with adults and children.

Some individuals are more prone than others to develop complications from influenza, e.g. bacterial pneumonia or other organ dysfunction. Severe influenza and complicated influenza potentially leading to hospitalisation and death are more likely to occur in vulnerable populations, such as older people (≥65 years of age), pregnant women, younger children (especially up to 24 months of age), and patients with chronic underlying diseases. These groups are considered at risk and represent the priority target for influenza vaccination programmes in the EU.

2.1.1. Epidemiology and risk factors, prevention

Influenza epidemics occur throughout the Northern Hemisphere and Southern Hemisphere during winter months. Worldwide, annual influenza epidemics result in about 90 million cases with approximately 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths, of which 28,000 to 111,500 occur in children. The main prevention strategy to minimize influenza burden is through annual prophylactic vaccination. Influenza vaccines are designed to protect against illness from the circulating virus strains, and the most commonly used vaccines have been inactivated influenza vaccines (IIV). The World Health Organization (WHO) recommends seasonal influenza vaccination for specific group of people which are more at risk of complications and death: pregnant women, elderly individuals (≥65 years of age), individuals with chronic medical conditions, health care workers, and children aged from 6 months to 5 years. Additionally, some public health authorities are moving towards vaccination strategies to reduce the risk of influenza in all age groups in an effort to decrease overall disease burden and spread to those in the population who are most at risk.

Traditionally and until 2012, seasonal influenza vaccines included antigens from 3 influenza strains in their composition, 2 influenza A strains (largely A/H1N1 and A/H3N2), and a strain from 1 of the 2 influenza B lineages (B/Yamagata or B/Victoria). This is because the majority of global influenza disease cases in humans since 1977 have been caused by circulating A/H1N1, A/H3N2, and influenza B strains viruses. Influenza B strains from the 2 lineages have co-circulated yearly since 1980s, when they emerged, with either or both types prevalent within any given year with no cross protection between the lineages.

The difficulty of choosing the correct B lineage to include in influenza vaccine formulations raises the possibility of a mismatch between the influenza B strain contained in the influenza vaccine and the influenza B strain predominantly circulating in the community in any given season, which for the northern hemisphere seasonal influenza vaccines occurred in 5 of the 10 influenza seasons 2001/2002 to

2010/2011. In order to avoid vaccine mismatch, quadrivalent influenza vaccines that include influenza B strains from both lineages have been recommended and these are expected to provide protection against the additional B strain. The first QIV was approved in the United States of America (US) prior to the 2012/13 Northern Hemisphere influenza season. A US study estimated that, in a season with a B strain mismatch, availability of quadrivalent influenza virus vaccines could reduce annual influenza cases (range: 2200–970,000), hospitalizations (range: 14–8200), and deaths (range: 1–485) in the US.

QIVc is a quadrivalent vaccine including B strains of both lineages, and is therefore expected to improve protection in target populations, especially in children where significant disease due to influenza B strains occurs and the potential for vaccine B strain mismatch has existed with trivalent influenza virus vaccines. QIVc is manufactured through cell-based manufacturing processes that are consistent with those used for the US-approved TIVc, Flucelvax, and the formerly (until June 2017) EU-approved TIVc, Optaflu.

2.1.2. Aetiology and pathogenesis

The influenza virus is an orthomyxovirus that can be classified into 3 biologically similar, but antigenically different types, A, B, and C, of which type A and B viruses are the most clinically significant. The influenza type A virus can be further divided into subtypes based on the hemagglutinin (HA) and neuraminidase (NA) surface glycoprotein antigens. The subtype refers to major antigenic variation with respect to the HA and/or NA virion antigens. Of the influenza type A virus subtypes, the A/H3N2 and A/H1N1 subtypes are the most clinically important for annual influenza disease burden. Influenza type B viruses show extensive variation in antigenicity. Although no true B subtype is known to exist, during the early part of the 1980s, 2 antigenically and genetically distinct lineages of influenza B emerged: B/Yamagata and B/Victoria.

The 3 influenza virus types share no common virus-coded antigens and differ in epidemiology and to some degree in the severity of illness caused.

2.1.3. Management

There is no effective treatment for influenza, and clinical management is based mostly on symptomatic treatment. Few antiviral drugs are available which may be able to reduce disease severity and duration, but they need to be taken soon after infection in order to be effective and can induce drug-resistant mutants. Influenza antivirals target the viral NA protein (zanamivir and oseltamivir), or the M2 protein (amantadine and rimantadine). The latter two are no longer recommended due to high level of resistance (>99%) in circulating viruses since 2009. Viruses resistant to the NA inhibitors have also increased dramatically after 2007 with the majority of seasonal H1N1 viruses (pre-pandemic 2009) exhibiting oseltamivir resistance.

Influenza can be complicated by bacterial superinfections, which are managed by specific treatments.

The most effective tool against influenza is prevention by vaccination. Influenza virus is known for its antigenic variability, essentially at the level of the surface proteins HA and NA, which is mostly driven by the selective pressure of the immune system on the virus quasispecies that is infecting an individual. This mechanism is due to the selection of genetic mutations in the viral genes and it's called antigenic drift. This is the reason why vaccines against seasonal influenza may need to be updated in composition on a yearly basis to include the latest circulating viruses and why people need to get vaccinated accordingly.

TIVc was approved in the EU in June 2007, under the tradename of Optaflu. One 0.5 mL dose of TIVc contains approximately 15 µg HA from each of the 3 influenza strains – A/H1N1, A/H3N2 and B (either Victoria or Yamagata lineage). TIVc was approved by the FDA in November 2012, for use in adults ≥18

years of age. The age indication for the US-licensed TIVc was extended in May 2016 for use in children ≥4 years of age.

QIVc was approved in the US in May 2016 via the accelerated approval pathway for use in adults and children of ≥4 years, with the post-approval requirement to conduct a paediatric absolute efficacy study.

QIVc and TIVc were originally developed and marketed by Novartis Vaccines and Diagnostics GmbH (NVD). In 2015 the influenza business was acquired by CSL, whose bioCSL arm was merged with the influenza vaccines division of Novartis to form Seqirus. In December 2016 the marketing authorization for Optaflu was transferred to Seqirus GmbH. The registration for Optaflu expired in June 2017 for commercial reasons, so TIVc is no longer authorised in Europe.

About the product

Flucelvax Tetra (also named QIVc throughout this document) is a quadrivalent surface antigen, inactivated, influenza vaccine, prepared in MDCK cell cultures. The active substance comprises virus surface antigens (hemagglutinin and neuraminidase) of the 4 strains of influenza virus recommended annually by the WHO for the Northern Hemisphere season:

- a strain A (H1N1);
- a strain A (H3N2);
- a strain B (Yamagata lineage);
- a strain B (Victoria lineage).

Influenza vaccines induce antibodies that protect against infection by influenza viruses that match or are similar to the antigen composition of the vaccine based on antigenic similarity of vaccine to circulating strains.

QIVc is manufactured using a suspension of a Madin Darby Canine Kidney (MDCK) cell line, rather than in embryonated hen eggs as with traditional influenza vaccine manufacturing. One 0.5 ml dose of QIVc consists of a sterile suspension for intramuscular injection containing approximately 15 µg HA from each of the 4 influenza strains (A/H1N1, A/H3N2, and B strains from both Victoria and Yamagata lineages; 60 µg in total). QIVc will be available in a single dose prefilled syringe presentation.

The cell-based production process of "on demand" suspensions of cells is maintained in a closed, sterile system during all production steps, and is based on a mammalian rather than avian cell line and therefore may lead to better antigenic matching with circulating human strains. The shift from eggs to cell culture allows work directly with wild-type viruses, avoids the generation of egg-adaptive mutations in the HA protein, increases surge capacity in the event of a pandemic, and provides better manufacturing control through a closed-system fermentation process. Furthermore, the use of a mammalian cell line for viral replication is a serum-free manufacturing process and removes the use of antibiotics. QIVc is produced using the same manufacturing platform as TIVc.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a suspension for injection in pre-filled syringe containing 15 mcg HA/strain/0.5 ml dose of purified virus surface antigen of each of the four influenza strains as follows:

Type A (H1N1), Type A (H3N2), Type B (Yamagata Lineage) and Type B (Victoria Lineage). The virus strains are chosen in compliance with the official annual strain recommendation from the WHO and CHMP.

Other ingredients are sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate, potassium dihydrogen phosphate and water for injections. The vaccine does not contain a preservative.

The product is available in pre-filled syringes (type I glass), with a plunger stopper (bromobutyl rubber) and packaged in sizes of 10 pre-filled syringes, without needle.

2.2.2. Active Substance

General information

The active substance consists of four monovalent bulks of purified virus antigen of influenza strains, Type A (H1N1), Type A (H3N2), Type B (Yamagata Lineage) and Type B (Victoria Lineage).

The active substance is composed of hemagglutinin (HA) and neuraminidase (NA) from each of the four influenza virus strains that are recommended every year by the WHO and CHMP. Influenza A viruses are divided into subtypes based on the HA and NA glycoproteins on the surface of the virus. Influenza B is comprised of two genetic lineages – Yamagata and Victoria. Strains of influenza A and influenza B viruses change as they evolve in humans. Each year, the four strains used in the seasonal quadrivalent influenza vaccine consist of one Influenza A (H1N1) virus, one Influenza A (H3N2) virus, one influenza B (Yamagata lineage) virus, and one influenza B (Victoria lineage) virus. For the purposes of this MA, the AS comprises influenza virus surface antigens (HA and NA) in compliance with the WHO and EU recommendation 2017/18.

The active substance is a suspension containing predominantly the purified outer membrane proteins, hemagglutinin (HA) and neuraminidase (NA), of each of the selected influenza virus.

HA is a cylindrically-shaped trimer ~135Å long that varies between 35 and 70 Å in diameter. Each trimer is composed of three identical subunits. The trimer has a central α–helical coil that forms the stem-like domain, and three globular heads, which contain the sialic acid binding sites. Each subunit consists of two disulfide-linked fragments (HA1 and HA2), which are cleaved from an intact precursor (HA0) by host proteases; this is the antigenically active form of HA. The HA antigen in the active substance is purified from viral membranes and therefore, includes a transmembrane region and a small C-terminal cytoplasmic domain.

NA forms tetramers that have four co-planar globular heads, a stalk, and an N-terminal hydrophobic transmembrane region. The NA antigen is purified from viral membranes and cleaves terminal sialic acids from carbohydrates on glycoproteins.

Traces of viral envelope proteins may be present. Each active substance is prepared from an influenza virus strain propagated in a suspension of culture-adapted Madin Darby Canine Kidney (MDCK) cells. The active substance from each of the four selected viral strains is combined to produce the quadrivalent final bulk vaccine. The HA and NA proteins used to produce the vaccine are intended to elicit a serological immune response to each of the subtypes included in the vaccine.

Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Monovalent bulk active substance is produced at Seqirus, Inc., Holly Springs, NC, USA. Seqirus, Inc. has been inspected between 27 June and 3 July 2018 by an EU/EEA inspectorate and a GMP certificate has been issued by the Finnish Medicines Agency on behalf of the EMA.

The active substance in the manufacture of the product comprises each of the four flu cell culture (FCC) monovalent bulks. Each FCC monovalent bulk is prepared by propagation of influenza working seed virus in MDCK cell suspension cultures. Cell expansion for the upstream non-infectious manufacturing process is conducted in cell culture medium, which is a chemically defined medium. Virus propagation for the upstream infectious manufacturing process is conducted in protein free medium. Following virus propagation, the virus/cell harvest is processed to remove cells and cell debris.

In the downstream manufacturing process, clarified harvest is purified and buffer exchanged by chromatography and tangential flow filtration and the whole virus concentrate is inactivated using β-propiolactone (BPL). Next, viral surface antigens are preferentially solubilized with the detergent followed by separation of the solubilized surface antigens from the viral core proteins. The process concludes with removal of detergent and buffer exchange of the surface antigens into the final formulation buffer yielding the influenza subunit HA and NA monovalent bulk.

The Flucelvax tetra active substance manufacturing process has been adequately described. The range of critical process parameter and the routine in-process controls along with acceptance criteria are described for each step. The active substance manufacturing process is considered acceptable. No reprocessing steps have been claimed.

Control of materials

Seed viruses

For influenza vaccines, the virus strains provided by the WHO collaborating centres are considered the candidate vaccine viruses (CVV); therefore they are the reference seed from which the working seed lots are prepared.

The applicant states that the CVVs are acquired from the WHO collaborating centres. The CVV can be isolated in eggs or directly in qualified cell lines, in line with the WHO document *"Antigenic Characterization of Seasonal Influenza Viruses Isolated in Vaccine-qualified Cell Lines"*, published in 2015. This document describes the antigenic and genetic characterization of the cell culture candidate vaccine viruses (ccCVV) and makes reference to the adventitious agent safety evaluation of these ccCVV.

Regarding the working seed virus, the applicant uses the same manufacturing process and control strategy for producing seed stock for both egg- and cell-derived CVVs. This is found acceptable, as long as the CVV obtained from the WHO collaborating centre has been suitably evaluated after receipt, to confirm it is antigenically identical to the CVV. Release criteria and in-process controls for testing of the working virus seeds have been provided. All test methods are considered validated and validation reports are provided.

Cell Substrates

The source and history of the MDCK cell line are well described and the testing performed is in accordance with the Ph. Eur. chapter 5.2.3. The qualification of the MDCK master and working cell banks has been performed including adventitious agent testing according to the current regulatory guidelines, and is found acceptable.

Cell bank qualification has been conducted according to state-of-the-art, which is endorsed. Additional working cell banks will be routinely prepared from the MCB according to a specified protocol and agreed specifications.

The MDCK cells themselves do not cause any risk of transmitting TSE as they are derived from dogs, which are recognized and excluded from the European TSE note for guidance (EMEA/410/01) as animals not being naturally susceptible to TSE. With regard to media components, the use of human- and animal-derived media components has been extensively investigated and their TSE-associated risk is found to be negligible.

Media, Solutions, and Raw Materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

No human or animal-derived materials are used.

Control of critical steps and intermediates

The control strategy initially presented by the applicant was not clearly understood. However during the MAA procedure, acceptable information on the control strategy in place has been provided by the applicant. The applicant has defined the different types of controls that were mentioned in the dossier and has explained the differences between them. This proposal is considered acceptable.

In conclusion, the control system is considered adequate to monitor and control the active substance manufacturing process with regards to critical, non-critical operational parameters and in-process controls. Actions taken if limits are exceeded are specified. The methods used for the control of critical steps and intermediates have been described and validated.

Process Validation and/or Evaluation

All process validation activities have been successfully completed according to the active substance process validation master plan. It was demonstrated that the FCC active substance manufacturing process meets established pre-determined criteria.

To ensure that the process remains in a validated state during commercial manufacturing, a continuous process verification (CPV) scheme has been established.

The validation of the virus seed stock production process was performed, operating parameters were within their normal operating ranges and performance parameters met all acceptance criteria. Based on this assessment, the data confirm that the virus seed production process was successfully validated and can reproducibly produce material that meets acceptance criteria. The process validation report for the virus seed production manufacturing process is provided.

This approach is considered to be acceptable.

The applicant has indicated that the annual strain variation will comprise data from annual strain optimisation activities including infection bioreactor optimisation, inactivation and splitting optimization in accordance with the Guideline on Influenza vaccines – Quality module (EMA/CHMP/BWP/310834/2012 Rev.1). The applicant has further committed to provide splitting conditions used for each strain in the commercial finished product as a post-authorisation commitment and routinely in each annual update. This is acceptable.

The respective lifetimes for chromatographic resins and ultrafiltration/diafiltration membranes were provided.

Container/closure integrity testing for the final active substance container closure system was performed. The outcome confirmed that the validation requirements were fulfilled and thus the process validation was acceptable.

Manufacturing process development

Development of this cell-based influenza vaccine was started by Behring Vaccine GmbH & Co (Marburg, Germany), later named Chiron Behring GmbH & Co KG (Chiron Vaccines) and then Novartis Vaccines and Diagnostics (NV&D/Novartis Vaccines). In 2015 Novartis Influenza Vaccines was acquired by CSL. Subsequently, the bioCSL arm of CSL group was merged with the influenza vaccines division of Novartis. The new corporate entity is referred to as Seqirus. Several documents included in the dossier still bear the names of Seqirus predecessor companies.

Holly Springs Process Development and Comparability between Marburg and Holly Springs

The process was scaled up two-fold at the Infection Bioreactor step and another passage was added to the cell expansion. No equipment was transferred from Marburg to the Holly Springs site; therefore, all equipment was purchased specifically for use in the scaled-up process and is appropriate for its intended use.

The process performance comparability was assessed by analyses of the data generated through routine manufacturing, in-process testing and release testing of monovalent bulks. The exact same three virus strains from each of the strain types (A/H1N1, A/H3N2 and B) used during process validation in Marburg were used at Holly Springs. To demonstrate comparability of the process performed at Holly Springs and the process performed at Marburg, performance attributes (output parameters) had to meet the pre-determined acceptance criteria during the three representative, consecutive seasonal GMP lots (e.g. PPQ batches) produced in Holly Springs and Marburg with the three virus strains A/H1N1, A/H3N2 and B.

The process performance comparability successfully demonstrated that the seasonal FCC vaccine monovalent bulk manufactured in Holly Springs, NC is comparable to the seasonal FCC vaccine monovalent bulk manufactured in Marburg, Germany with regard to performance attributes (output parameters).

Analytical Comparability

The critical process parameters and quality attributes did not change for demonstration of comparability from Marburg to Holly Springs. The exact same three virus strains from each of the strain types (A/H1N1, A/H3N2 and B) used during process validation in Marburg was used at Holly Springs for the analytical comparability analysis.

The analytical comparability successfully demonstrated that the seasonal FCC vaccine monovalent bulk manufactured in Holly Springs, NC is comparable to the seasonal FCC vaccine monovalent bulk manufactured in Marburg, Germany with regard to release and in-process test results.

In conclusion, Marburg and Holly Springs can be considered comparable manufacturing sites for the production of influenza cell culture seasonal monovalent bulk antigen. In addition, both manufacturing sites have been successfully validated for commercial manufacturing.

Process Performance Comparability between Line 1 and Line 2 at Holly Springs

The manufacturing process was validated at scale on manufacturing Line 1 and licensed in 2014 for production of Flucelvax in the United States (US). Line 2 was validated and licensed in 2015 for the

production of influenza cell culture (FCC) vaccine monovalent bulk. For the purposes of process performance qualification (PPQ), three consecutive upstream infectious production runs using the B virus strain and one run using each of the representative H1N1 and H3N2 strains were successfully executed. The B virus strain was selected to be run in triplicate, as B types are historically more challenging with regard to productivity and the ratio of impurities to HA content.

Process performance comparability of Line 1 to Line 2 was demonstrated using the B type, as this was to be run in triplicate on Line 2. Seven representative cGMP lots previously produced in Holly Springs on Line 1 for the B virus strain type were used for comparison to the B virus strain type lots manufactured during the PPQ on Line 2.

Analytical Comparability between Holly Springs Line 1 and Line 2

Analytical comparability evaluated 9 monovalent bulks (3 of each seasonal strain) from the validated Line 1 process to 4 monovalent bulks produced on Line 2 (1 H1N1 Lot, 1 H3N2 Lot, and 2 B-Strain Lots). The exact same three (3) virus strains from each of the strain types (A/H1N1, A/H3N2 and B) used during process validation on Line 1 were used on Line 2 for the analytical comparability analysis.

Process Performance Qualification –Holly Springs Line 2

The PPQ provided assurance that the seasonal FCC vaccine monovalent bulk manufacturing process (Process 1.1) on Line 2 at Holly Springs could be executed in a consistent manner and produce FCC monovalent bulk meeting the specified quality attributes. The seasonal FCC vaccine monovalent bulk PPQ was successfully performed using three virus strain types (A/H1N1, A/H3N2, and B) as per approved protocols.

Characterisation

Elucidation of structure and other characteristics

The applicant presented the characterisation of monovalent FCC bulks. It was agreed that no further characterisation studies are considered necessary.

In addition, detailed analyses of the physicochemical and biological properties of the FCC-derived HA proteins have been conducted. A number of physicochemical studies were also conducted with the NA proteins.

The presence of HA in both the active substance and finished product has been confirmed. The presence of NA is confirmed by an identity test.

Impurities

The applicant has provided an analysis of potential product-related impurities (e.g. aggregates, fragments, etc.). A convincing rationale has been included that explains why the product-related impurities found in the vaccine bulks that correspond to higher-order structures of the HA protein do not represent a concern. It can be considered that these higher order oligomers of HA are the preferred presentation in the influenza vaccine as they elicit a strong immunogenic response.

On the basis of these data and the comparison drawn to the same antigens present in the trivalent Agrippal, the characterisation is considered adequate to confirm the expected structure of purified virus antigen of influenza strains, Type A (H1N1), Type A (H3N2), Type B (Yamagata Lineage) and Type B (Victoria Lineage).

Potential process-related impurities have been adequately identified by the applicant. The Optaflu (TIVc) manufacturing process has already demonstrated the capability to reduce the level of these impurities. As

the QIVc manufacturing process has been confirmed to be the same as the TIVc with the exception that an additional influenza B strain (an additional monovalent bulk) is prepared, no additional information is required.

Specification

The active substance release specification is expressed for the combination of the four monovalent strains into a quadrivalent formulated bulk. The set of specifications cover identity, purity and potency. The proposed testing protocol for the monovalent bulk complies with the Ph.Eur. monograph. Potency of the active substance is determined by the quantification of the haemagglutinin antigen using the single radial diffusion (SRD) assay.

The analytical procedures (principle, equipment, standards/solution, procedure, measurement/ evaluation) are concisely described and the validation reports provided.

Additional information was also requested for some of the methods.

In summary, the release specifications, as proposed by the applicant are considered acceptable as they cover the main characteristics of the product.

Batch analysis

Batch analysis results demonstrate that the monovalent bulk production process is consistent.

Reference Standards or Materials

Reference standards have not changed from the already approved ones.

Container Closure System

The monovalent bulk is stored in a 50-L polypropylene (PP) carboy with a stainless-steel dip-tube system integrated into a white polypropylene screwcap closure fitted with a silicone gasket.

Stability

The choice of the tested parameters has been accepted because they are stability-indicating parameters as verified in the forced degradation studies.

The stability data is considered appropriate to support the proposed shelf life and the post-approval stability protocol and stability commitments are also acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description and composition of the product

Flucelvax tetra contains hemagglutinin (HA) and neuraminidase (NA) surface antigens from each of the four influenza strains recommended annually by the WHO and CHMP.

The finished product is presented as a clear to slight opalescent liquid for injection. The vaccine is supplied in a pre-filled syringe ready for use. Each syringe is intended for single use.

The formulation is prepared to contain the minimum dose of 15 µg hemagglutinin antigen from each of the four virus strains. The antigens are diluted in a clear, sterile, buffered aqueous solution. Excipients are

sodium chloride (isotonic), potassium chloride (isotonic), magnesium chloride hexahydrate (stabilizer), disodium phosphate dihydrate (buffer), potassium dihydrogen phosphate (buffer) and water for injections (diluent) and comply with Ph.Eur.

A sufficient overfill is included in the syringe to ensure the withdrawal of a nominal volume of 0.5 mL per human dose.

The composition of the QIVc finished product is also the same as the previously EU-licensed Optaflu TIVc, except for the addition of a second B strain.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph.Eur. standards. There are no novel excipients used in the finished product formulation.

The primary packaging is described as pre-filled syringes (type I glass), with a plunger stopper (bromobutyl rubber) packed as sizes of 10 pre-filled syringes, without needle. The material complies with Ph.Eur. and EC requirements and the choice of container closure system has been validated by stability data and is adequate for the intended use.

The information on the description of the finished product presented is considered acceptable.

Manufacturing process development

The Holly Springs manufacturing site has been producing and commercially distributing Flucelvax Quadrivalent to the US market since 2016.

Manufacture of the product and process controls

The finished product is released at Sequirus Vaccines Ltd, Gaskill road, Speke, Liverpool, L249GR, UK.

Manufacturing Process

The manufacturing process includes blending of monobulk lots of four strains and dilution with buffer to produce the quadrivalent bulk vaccine. For the filling process, the formulated bulk product tank is aseptically connected to the sterilizing filter and the product is passed through a filter prior to being filled into syringes. The syringes are closed with a bromobutyl plunger and the syringe tubs are labelled with batch-specific information.

The filling process has been validated and appropriately described. The primary packaging of the finished product, a 1 ml syringe and a bromobutyl plunger, has been validated and the inspection, labelling and packaging procedures are all found to be acceptable.

Batch Formula

The HA concentration for each strain varies and is calculated using an agreed procedure for the determination of the strain-specific blend target.

Process Controls

The manufacturing process is controlled through critical process parameters, in process testing and release testing. A summary of the critical process parameters and tests for the finished product is provided.

Release testing is performed on the filled product. The release specification for filled product must be met for batch release.

In conclusion, the applicant has provided a complete manufacturing process description including a general flow chart containing process parameters and in-process controls for each step. The critical steps, critical process parameters and in-process controls have been clearly identified.

Process validation

For Flucelvax tetra finished product formulation step, various validations and formulation process-associated studies were performed at Holly Springs. To support licensure of the QIVc fill finish process at Holly Springs, various validations and associated studies for the filling and packaging processes were performed.

In conclusion, the validation protocols and results are considered satisfactory. In-process hold times during the formulation steps have been justified and the validated duration for the aseptic process has been clearly indicated. The applicant presented the validation for the batch scale hold times in the formulation vessel. The provided data are sufficient to validate a hold time for the batch scale product. A shipping validation was performed.

The container closure integrity has been validated.

An extractables study was performed to identify and to estimate the amount of compounds that may be extracted for QIVc syringes upon contact with model solvents.

The amount of leachables detected in Flucelvax tetra stored in pre-filled syringes during the 12-month study period were analysed and determined to be below the established safety thresholds for the safety concern threshold/parenteral/ophthalmic finished products (SCT/POPD) for leachables or the parenteral permissible daily exposure (pPDE) levels.

Tungsten and vanadium are present at levels which would not result in a toxicologically-relevant increase in body burden. No local or systemic toxicity would be expected from sporadic exposure to the leachables at the levels detected. The applicant has provided the quantitative results of the leachables measured in the stability study. In summary, the data shown confirm that there are no toxicological concerns for the leachables.

Microbiological attributes

The finished product is a sterile parenteral solution. No preservatives are used in the finished product.

Both formulation and filling of the syringes are carried out in controlled conditions, and the filled final product is tested for sterility. Moreover, the integrity of the container closure system for the syringes to prevent microbial contamination is confirmed by the stability studies for the product which include sterility tests and the container closure integrity test. Nonetheless, results of a microbial ingress study were asked to be presented, unless appropriately justified, to confirm the suitability of the container closure system to maintain microbial sterility. The results submitted confirm the suitability of the container closure system to maintain integrity with respect to microbial sterility.

Product specification

The release and shelf life specifications for release of Flucelvax tetra final bulk vaccine and final lot have been provided.

The finished product specification was subject to CHMP Scientific Advice (EMEA/H/SA/2628/1/FU/1/2017/III). The CHMP considered the proposed FP specifications acceptable with further justification requested on their limits in accordance with the relevant guidance (ICH Q6B).

During the procedure the applicant provided additional justification for the FP specifications, which has been accepted. The chosen specifications and their limits are considered justified and accepted.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines. Of the analytical procedures used for the release of the final bulk vaccine lots and final lots, three are non-compendial methods: total DNA content, hemagglutinin antigen and non-hemagglutinin protein.

The total DNA content is determined. Single radial immunodiffusion (SRD) is used to determine hemagglutinin (HA) antigen concentration (titre). The quantitative determination of protein content is performed.

The non-compendial analytical procedures for the release of the final bulk vaccine and the filled lot have been validated or verified according to the relevant guidance from ICH or all test methodologies remain unchanged.

Validation summaries for the non-compendial methods and verification information for compendial methods are provided. Few issues related to these were raised during the procedure and adequately addressed by the applicant. The applicant has agreed to a post-authorisation recommendation.

Concerning the formulated finished product, the formulation target for each seasonal campaign is determined. The applicant has provided the formulation targets for the final bulk vaccine for the 2016/2017 and 2017/2018 campaigns. Of note, PPQ batches were all formulated. In addition, the applicant has been asked to ensure that the splitting conditions used for each strain in the commercial finished product are provided in the annual update as requested in the Guideline on Influenza vaccines – Quality module (EMA/CHMP/BWP/310834/2012 Rev.1).

Batch analysis

Batch analysis results comply with the specifications.

Reference materials

A list of reference standards used by the applicant in the different release methods has been provided. No reference standard for the vaccine itself is expected, as the composition is subject to change every year according to the official recommendations.

Stability of the product

The finished product can be stored for 12 months in a refrigerator (2°C – 8°C). The product should not be frozen and should be kept in the outer carton in order to protect it from light.

The stability studies in support of the proposed shelf life were carried out as follows:

- Process performance qualification lots
- Annual stability lots:

Stability studies were performed. In addition, stability data for the QIVc annual stability lots from the 2016/2017 and 2017/2018 northern hemisphere campaigns were included. The design of the stability studies and the number of lots placed on stability are considered adequate.

The analytical parameters assessed for stability are in agreement with ICH Q5C.

The long-term stability results for all Process Performance Qualification Lots met all acceptance criteria through study completion, when stored at 2-8°C. Thus, the results of the long-term stability studies support a shelf life of for the QIVc product, when stored at 2-8°C. The accelerated stability results are for information only and the stability profile observed is as expected.

Regarding the annual stability lots, the long-term testing has been completed for all five of the lots from the 2016/2017 season and continues to support a shelf life for the QIVc product, when stored at 2-8°C. For the lots of the 2017/2018 campaign placed on long-term stability, testing has been completed for the remaining lot. The applicant has updated the stability data for as long as there are results, which is considered acceptable.

The long-term stability results for all lots met all acceptance criteria through study completion when stored at 2-8°C.

Regarding the post-approval stability protocol and stability commitment, a minimum of production batches will be placed on stability at the recommended storage condition of 2-8°C and the same analytical parameters will be assessed as for the above mentioned lots each year following a change in vaccine composition in line with the WHO/CHMP recommendations.

In conclusion, based on the availably stability data, the shelf life of 12 months at 2°C – 8°C as stated in the SPC is considered acceptable.

Comparability exercise for finished medicinal product

See manufacturing process development.

Adventitious agents

The adventitious agent management program for the Flucelvax tetra has been set up in line with the ICH recommended complementary approach to controlling potential viral contamination of biotechnology products.

Viral safety

The MDCK cell line has been selected and tested for the absence of undesirable viruses which may be infectious or pathogenic to humans. The manufacturing process has been assessed for its capacity to clear infectious viruses. Product intermediates and the final container are tested at appropriate intervals to assure the absence of contaminating infectious viruses.

The quantitative assessment of a wide range of potentially relevant viral agents, with consideration of accidental contamination at different production stages, has demonstrated that the Flucelvax tetra vaccine manufacturing process is capable of eliminating substantially more virus than is estimated to be present in a single-dose equivalent of unprocessed bulk (in accordance with ICH Guideline Q5A). Even under worst-case conditions, the viral titres would be orders of magnitude below a single infectious dose and thus unable to cause infection. If a contamination event were to occur, more than 100,000 doses of the vaccine would need to be administered to one individual to accumulate a single human infectious dose of any of the agents considered.

Regarding the strategy of selecting PCR testing for some viruses and not for others, the applicant was asked to explain the discrepancy of active substance PCR testing results regarding RSV and parainfluenza virus. This discrepancy was due to a typographical error which has been corrected, and clarification was provided.

Overall, the viral safety package is comprehensive and provides assurance on the safe use of the vaccine.

TSE aspects

The manufacturing process does not contain any animal/human-derived components. All filters and membranes are free from animal-derived materials.

The TSE safety has been adequately addressed and is considered to be assured.

Post Approval Change Management Protocols

The initial Marketing Authorisation Application contained two post approval change management protocols(1) on the addition of contract manufacturing organisation (CMO) for filling, visual inspection and packaging technology transfer and (2) a plan to introduce a number of process changes for the manufacture of active substance.

Addition of CMO for Filling, Visual Inspection and Packaging Technology Transfer

The scope of this proposed post-approval change is to assess the technical transfer to add a CMO for the QIVc fill/finish process. Final bulk vaccine will be shipped to the CMO for filling. The formulation process will remain unchanged.

It should be kept in mind that the assessment given at this point only applies to the proposed theoretical package and that for approval, all the validation data will have to be presented by the applicant and evaluated in a variation procedure.

Provided that comparability can be demonstrated, the proposed changes can be approved.

Stability plan

The protocol contains a stability plan.

In addition to the process validation lots, production batches manufactured at will be placed on long-term stability at the recommended storage condition of 5°C±3°C, in accordance with the stability requirements detailed in 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment. This approach is found acceptable.

Active Substance Process Changes

The aim of this post approval change management protocol (PACMP) is to outline a detailed plan to demonstrate that the safety, quality, identity, purity and strength of the active substance are not adversely impacted due to the changes in the active substance manufacturing process.

To assess physicochemical comparability an evaluation will be done against pre-defined criteria through a quantitative and qualitative analysis of data to allow for an objective assessment of whether each version of the process are comparable. The comparability demonstration strategy will be carried out in line with ICH guideline Q5E.

In principle, all changes have been justified in the information provided by the applicant and are found to be acceptable.

This approach has been endorsed.

Stability Plan

As there are no changes planned for the formulation, filling, inspection, and packaging manufacturing processes, there is no plan by the applicant to perform process validation for finished product manufacture.

The proposed stability plan can be endorsed. All available data collected from the finished product stability study will be submitted as part of the Type IB variation.

Based on the proposed equipment change, no changes to the process outputs (i.e. performance attributes) are expected. To demonstrate comparability, all results generated must meet the pre-defined acceptance criteria for the process outputs.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In general, the applicant has adequately described and documented all parts of the Quality module of the dossier.

A major objection raised during the procedure in relation to the manufacturer of the finished medicinal product has been satisfactorily resolved. A GMP inspection carried out by the Finnish Medicines Agency on behalf of EMA turned out to be satisfactory. A valid GMP certificate has been issued dated 13 August 2018.

All the other concerns raised were mainly related to the description of the manufacturing process, which was described at high level without the required precisions and part of information only mentioned in the process validation. Moreover questions were raised on the proposed control strategy including the process validation and the control of active substance and finished product. The applicant was able to address all of them appropriately.

The applicant has included two Post Approval Change Management Protocols into the initial application. The protocols have been revised during the procedure and it has been specified which updated module 3 documents will be provided within the type IB procedures. In due time all the data and documents related to these procedures will be assessed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of Flucelvax tetra has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The CHMP has identified the following measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:

None

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant should determine the cross reactivity level between the two B strains and perform forced degradation studies to verify that the method is stability indicating.
2. The applicant should provide the formulation targets to be used for each commercial season.

3. The applicant should provide the splitting conditions used for each strain in the commercial finished product in the annual update.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant has based the pharmacology of the product in data obtained with the approved but withdrawn from the market trivalent (TIVc) formulations produced using the MDCK cell culture process. It is considered that TIVc studies are relevant to QIVc. Even though QIVc contains an additional antigen, the same drug substance is used in both vaccines, and the manufacturing process and excipients are the same. This change is not expected to modify the product pharmacology. This approach has been endorsed by EMA in ScAd requested by the applicant. In consequence additional studies would not provide relevant additional information for the non-clinical safety characterization of the QIVc vaccine. The pharmacology assessment for TIVc is deemed relevant for the assessment and therefore referenced in the non-clinical assessment report.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacological effect of the vaccine is the induction of antibodies to influenza antigens and protection against infection. Therefore, the demonstration of antibody induction (immunogenicity) and efficacy (protection in an animal model of influenza virus challenge) was the focus of the non-GLP nonclinical pharmacology studies.

Mouse immunogenicity studies were performed using the intraperitoneal (IP) route to demonstrate the comparability of MDCK-derived antigens to conventional egg-derived antigens of the same type.

Based on mouse immunogenicity results, MDCK-derived and conventional egg-derived antigens were comparable. In addition, the immunogenicity of the vaccine was dose-dependent. Haemagglutination inhibiting (HI) titres were lower following administration of 1/100th of the 15µg HA per strain clinical dose versus 1/10th of the 15µg HA per strain clinical dose.

Immunogenicity was also evaluated in the pivotal GLP toxicology study in which rabbits were given 2 intramuscular administrations of Optaflu, the reference vaccine Agrippal, or placebo. HI results for serum antibodies to two of the strains (A/New Caledonia and B/Guangdong) showed no titre pre-treatment and an increase in titre after the second vaccine dose of Optaflu or Agrippal. There were background titres against strain A/Panama in control animals and pre-treatment in Optaflu and Agrippal-treated animals, which were attributed to nonspecific binding. However, a trend towards increasing amounts of A/Panama antibody titre could be seen after the second vaccine dose.

Immunogenicity and protection against influenza virus challenge has also been demonstrated in ferrets, which are currently considered the best animal model for infection with human influenza viruses.

During the development of the ferret challenge model, two range-finding studies were conducted to evaluate various concentrations of the challenge virus to determine an appropriate dose for use in challenge studies. Subsequently, four non-pivotal challenge studies were performed using naive (unprimed) ferrets. In these challenge studies, ferrets were vaccinated twice with vaccine formulations, and then challenged with live virus homologous to the vaccine. These animals were immunologically naive (not primed with a heterologous virus). Although the vaccine formulations were well tolerated, the

immunogenicity and challenge results were highly variable. Relevant effects on endpoints such as temperature increase were only seen in one of these four studies; however, there were also low responders in the negative control group. There was no clear and consistent effect of vaccination, with the positive control vaccine or with the test vaccine. The lack of protection seen in these studies is consistent with published literature where naïve (unprimed) ferrets did not produce HA-specific antibody following immunization with concentrations of antigen shown to produce high titres of serum antibody and immunity in humans.

In the pivotal ferret study, animals (8 animals per group) were first primed intranasally with a heterologous virus (A/Panama/2007/99 [H3N2]), and then immunized twice with Optaflu (A/New Caledonian/20/99 [H1N1], A/New York/55/2004 [H3/N2], B/Jsiang/10/2003), a comparator vaccine (Agrippal) (based on the same antigens, also called positive control) or water (control). Two immunizations were given intramuscularly 3 weeks apart. Seven days after the second immunization, animals were challenged intranasally with live virus homologous to the vaccine (A/New Caledonian/20/99 [H1N1]). Vaccine efficacy was evaluated based on body weights, body temperatures (see below) and clinical symptoms. In addition, viral shedding, leukocyte counts, and antibody titres were assessed. In this study, Optaflu was considered comparable to Agrippal and differences between the two groups were not statistically significant. Both vaccines reduced viral shedding and prevented body temperature increase.

Other pharmacology studies

No dedicated studies were performed regarding secondary pharmacodynamic, safety pharmacology and pharmacodynamic drug interactions. This is endorsed due to the nature of the product and the available non clinical and clinical data.

2.3.3. Pharmacokinetics

No dedicated studies for the assessment of the pharmacokinetics of the product were performed. This approach is endorsed due to the nature of the product under evaluation.

2.3.4. Toxicology

In order to address the product toxicology the applicant has forwarded safety toxicology data obtained in vivo in animal studies dosed with the trivalent (TIVc) formulations produced using the MDCK cell culture process. It is considered that TIVc studies are relevant to QIVc. Even though QIVc contains an additional antigen, the same drug substance is used in both vaccines, and the manufacturing process and excipients are the same. This change is not expected to modify the product pharmacology. Clinical data provided do not suggest that the modification results in changes in the safety profile of the QIVc compared to TIVc. This approach has been endorsed by EMA in ScAd requested by the applicant. It is considered that additional studies would not provide additional information for the non-clinical safety characterization of the QIVc vaccine. The assessment of the TIVc is relevant for the assessment and therefore referenced in the non-clinical assessment report.

Single dose and repeat dose toxicity

No dedicated single dose studies were performed. Single-dose toxicity and local tolerability of TIVc was evaluated in rabbits following the administration of the first dose in the repeat dose toxicology study (Study No. 191-44). There was no evidence of systemic toxicity after a single dose based on in-life

evaluations. Since data from the TIVc is considered relevant for the assessment of the toxicity of the product TIVc, this TIVc is taken in consideration and included in this assessment.

The pivotal GLP study assessed the local and systemic toxicity of Optaflu in New Zealand White rabbits after two administrations and determined the reversibility of findings. Agrippal served as the reference article. Phosphate buffered saline (PBS) was the control article (placebo). The study consisted of three groups of 6 animals per sex per group. Rabbits received an intramuscular injection of 0.5 ml of either the test or reference article or placebo on Days 1 and 8. The two doses administered to rabbits in this study exceeded the intended number (one) proposed for annual interpandemic immunization and covered the intended number of doses (two) recommended for the paediatric population, more precisely in children from 4 to 9 years of age. Results showed that two intramuscular injections of the test article, Optaflu, given one week apart, were immunogenic and very well tolerated in test rabbits. There were no treatment related adverse effects on clinical observations, dermal scoring, body weights and temperatures, food consumption, clinical pathology (haematology, coagulation, and clinical chemistry), organ weights, or macroscopic evaluations. Histopathological evaluation revealed the expected reactions (necrosis and haemorrhage) at the injection sites, which were seen in all experimental groups, attributed to the intramuscular injection, and partially to fully resolved by the end of the recovery period.

Genotoxicity and carcinogenicity

No genotoxicity and carcinogenicity studies were carried out in line with relevant guidelines. Studies evaluating genotoxicity and carcinogenicity are normally not required for viral vaccines. Since no adjuvants or novel excipients are used in this product absence of those studies is considered acceptable.

Reproduction Toxicity

TIVc was shown to be immunogenic with no relevant effects on the reprotoxicity of the product. TIVc was administered in five doses to female NZW rabbits. No effects were seen on mating, fertility, gestation and lactation in the conditions of the assay. Furthermore no relevant concerns that could need additional non-clinical testing have been identified.

No juvenile toxicity was required for the assessment of the product. No differential toxicity or pharmacokinetics that could affect developing organs were reported furthermore clinical data available do not reveal concerns that would result in the need of toxicity studies in juvenile animals.

Toxicokinetic data

N/A

Local Tolerance

No dedicated studies were performed for the assessment of local tolerance. It is acceptable because local tolerance was evaluated during the pivotal repeat-dose toxicology study in rabbits (Study n°191-44). As the microscopic findings resolved by the end of the recovery period, they do not pose any safety issue.

Other toxicity studies

The tumorigenic studies performed on the MDCK cell culture manufacturing platform and assessed for the TIVc approval are applicable also for the QIVc as the manufacturing process is identical. The result of those studies was that only intact MDCK cells were tumorigenic but they are completely removed during the manufacturing process; therefore whole cells do not pose a risk in the final product. In addition the

clinical safety data and post-marketing data produced with the TIVc indicate no risks when administered to patients.

2.3.5. Ecotoxicity/environmental risk assessment

No concerns are expected for the environment as a result of the product administration to humans. Proteins from the influenza virus naturally circulate in the environment, and the strains used in the vaccine formulation are naturally occurring viruses. Protein vaccines are normally exempted from the requirement to conduct environmental risk assessment studies as specified in the relevant guideline. Consequently, the lack of ERA studies is acceptable.

2.3.6. Discussion on non-clinical aspects

QIVc is produced based on the same manufacturing process as the TIVc previously authorised, Optaflu. The addition of antigen from a second B strain is not expected to alter the pharmacological effect (immunogenicity and protection), nor the toxicity profile of the vaccine. Consequently, no additional non-clinical studies were performed with QIVc in addition to those conducted with the TIVc, which are considered supportive and were previously assessed by the CHMP in the context of MAA for Optaflu. This strategy was already reviewed by the CHMP during pre-authorisation scientific advices and it remains acceptable for the reason stated above.

The vaccine was shown to be immunogenic in mice, rabbits add ferrets by means of HI and neutralising antibodies and the responses were comparable to those induced by conventional egg-produced influenza vaccine. Challenge studies in ferrets indicated that despite some flu-like symptoms animals were protected against disease as compared to un-vaccinated controls. There was no statistically significant difference with the TIVc comparator.

The toxicology studies included evaluation of local tolerance, single dose and repeated dose toxicity and reproductive and developmental toxicity. The vaccine was well tolerated and there was no evidence of systemic toxicity other than the expected reactions (necrosis and haemorrhage) at the injection sites, which were also seen in the placebo groups and were attributed to the intramuscular injection, and partially or fully resolved by the end of the recovery period. No effects were seen on mating, fertility, gestation and lactation and in general no relevant concerns that could need additional non-clinical testing.

No safety pharmacology, genotoxicity and carcinogenicity studies were carried out in line with relevant guidelines and this is considered acceptable based on the vaccine formulation. The vaccine is unadjuvanted and the excipients are not novel with respect to what is generally included in vaccines, for which there is a large clinical experience. The cell culture manufacturing platform was already established for TIVc, for which was concluded that a risk of tumorigenicity is limited to whole MDCK cells that are completely removed from the final product.

The TIVc formulation used in the non-clinical studies was representative of the TIVc clinical lots. On a body weight basis, multiples of the highest anticipated QIVc clinical dose of antigen, residuals, and impurities were administered in the toxicology studies, hence the amounts of TIVc delivered in the studies accounted for the additional antigen included in QIVc.

No relevant issues are outstanding as a result of the non-clinical assessment of the product.

Assessment of non-clinical aspects relevant for paediatrics

No signs of differential toxicity or pharmacokinetics that could affect developing organs were reported in in embryofoetal and post-natal development. The repeat-dose toxicology studies tested 2 doses in line

with the intended indication in children below 9 YOA with no previous vaccination, and showed no safety concerns.

No juvenile toxicity studies were conducted, which is considered acceptable given the type of product and the lack of toxicity and the availability of favourable clinical data. Juvenile toxicity studies are generally no longer required by current guidelines (see EMA influenza guideline and WHO GL on NC of vaccines). The available safety clinical data do not reveal concerns in children, and administration of the vaccine results in the same pharmacological effect (induction of antibodies) in children and adults.

2.3.7. Conclusion on the non-clinical aspects

Based on the data available from studies conducted with TIVc, the product is considered approvable from a non-clinical perspective. Moreover, clinical safety results from clinical studies (V130_01 and V130_03) (conducted with the QIVc versus the TIVc) allow to admit that the QIVc product has an acceptable safety profile in adult and paediatric populations. Of note, no specific paediatric safety concern has been reported (see clinical safety part of the assessment report).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Summary of the studies included in the application

Study, Season	Study Objectives	Population	Number Subjects Exposed to QIVc or TIVc	Number Subjects Exposed to Comparator	Follow-up Period
QIVc					
V130_01 US 2013-2014 NH	safety, immunogenicity	healthy subjects ≥ 18 years	1334 QIVc 1346 TIV1c+TIV2c	TIV1c, 677 TIV2c ,669	6 months
V130_03 US 2013-2014 NH	safety, immunogenicity	healthy subjects 4 to < 18 years	1159 QIVc 1173 TIVc+TIVc2	TIV1c, 593 TIV2c, 580	6 months
TIVc					
V58P1 Germany 2001/2002 NH	safety, immunogenicity	healthy subjects ≥ 18 years	120	TIVeA, 120	3 weeks
V58P2 New Zealand 2003 SH	safety, immunogenicity	healthy subjects ≥ 18 years	110	TIVeA, 113	3 weeks

Study, Season	Study Objectives	Population	Number Subjects Exposed to QIVc or TIVc	Number Subjects Exposed to Comparator	Follow-up Period
V58P4 Poland 2004-2005 NH	safety, immunogenicity	healthy subjects ≥ 18 years	1330	TIVeA, 1324	6 months
V58P4E1 Poland 2005-2006 NH	safety, immunogenicity	healthy subjects ≥ 18 years	1104	TIVeA, 1131	6 months
V58P4E2 Poland 2007-2008 NH	safety, immunogenicity, revaccination, concomitant pneumococcal vaccine administration	healthy subjects ≥ 18 years	1108	TIVeA, 414	6 months
V58P5 US 2005-2006 NH	safety, immunogenicity	healthy subjects 18 to < 50 years	309	TIVeF, 304	6 months
V58P9 Lithuania 2005-2006 NH	safety, immunogenicity, lot-to-lot consistency	healthy subjects 18 to < 61 years	1028	TIVeA/F, 171	6 months
V58P12 US, EU 2007-2008 NH	safety, immunogenicity	healthy subjects 3 to < 18 years	2251	TIVeF, 1329	6 months
V58P13 US, Finland, Poland 2007-2008 NH	safety, clinical endpoint efficacy, immunogenicity	healthy subjects 18 to < 50 years	3813	TIVeA, 3669 Placebo, 3894	6 months
V58P15 Italy, Spain 2013-2014 NH	safety	Subjects at risk for influenza related complications 3 to < 18 years	278	TIVeA, 148	6 months
V58_23 US 2014-2015 NH	safety, immunogenicity, lot-to-lot consistency	healthy subjects 18 to < 50 years	1170	TIVeF, 390	3 weeks
V58_31 Australia, New Zealand, Philippines Thailand 2013 SH 2013-2014 NH	safety	healthy subjects 4 to < 18 years	1370	TIVeF, 682	6 months

Abbreviations: NH = northern hemisphere; QIVc = cell-based quadrivalent influenza vaccine; SH = southern hemisphere; TIVc = cell-based trivalent influenza vaccine; TIVeA = egg-based trivalent influenza vaccine (Agrippal); TIVeF = egg-based trivalent influenza vaccine (Fluvirin)

2.4.2. Pharmacokinetics

Pharmacokinetics studies were not conducted for Flucelvax Tetra, in line with current guidelines. Pharmacokinetic studies (including bioavailability and bioequivalence studies) are not required for vaccines as the kinetic properties of vaccines do not provide relevant information for establishing adequate dosing recommendations.

2.4.3. Pharmacodynamics

Mechanism of action: QIVc provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine by inducing humoral antibodies against the haemagglutinin proteins. These antibodies neutralise influenza viruses.

The pharmacodynamic profile of vaccines is defined by their immunogenicity profile, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

For each vaccine strain, anti–HA antibody titres were measured using the serological haemagglutination inhibition (HI) assay. All sera were tested by a validated HI assay performed at the same laboratory (Novartis Vaccines and Diagnostics GmbH Clinical Serology Laboratory in Marburg, Germany) on working seed level, and was based on the method described in Palmer et al. (1975) and WHO (2002).

The HI assay in both QIVc studies was performed using cell-based test antigens; in the TIVc studies, egg-based test antigens were used in studies V58P13, V58P4, V58P9, V58P4E1, and V58P4E2. Both cell-based and egg-based test antigens were used in studies V58_23 and V58P12: this was because mammalian cell-based antigens should be antigenically more similar to the human virus than egg-based antigens, and the most appropriate measure to quantify antibodies induced by the cell-based vaccines may be the cell-based test antigen.

At the time the studies presented in this application were planned and executed, the assessment of the immunogenicity of influenza vaccines was traditionally based on the HI assay, and the HI antibody response was considered an acceptable surrogate marker of activity reasonably likely to predict clinical benefit. No other measurements now recommended in new CHMP guideline for influenza vaccines (EMA/CHMP/VWP/457259/2014; for example virus neutralization, single radial haemolysis, cell-mediated immunity, antigen-specific T-cell frequencies, CD4+ and CD8+ responses, activation of memory B cells, or evaluation of anti-neuraminidase antibodies) were investigated in these studies. In the QIVc pivotal immunogenicity studies, the possibility to conduct additional immunogenicity analyses by MN, anti-NA, SRH and HI for heterologous influenza strains was included in the protocol as exploratory endpoint, but such investigations were not performed. This is considered acceptable in these circumstances and in view of the fact that the applicant will assess neutralising antibodies in the ongoing QIVc efficacy study V130_12 (subjects 2-18YOA) and in the 2 planned QIVc studies V130_10 and V130_14 (respectively immunogenicity and absolute efficacy in subjects 6-47 months of age).

In all studies of the QIVc and TIVc clinical development program, serology was assessed at baseline (i.e. before vaccination) and at 3 weeks after the last vaccination, which is approximately when the HI antibodies reach their peak in human sera (Kunzel et al. 1996). Persistence of antibodies was assessed at 6 months after vaccination in study V58P9, and at 1 year after vaccination in subset of subjects from study V58P4 who were enrolled in study V58P4E1.

2.4.4. Discussion on clinical pharmacology

The haemagglutination inhibition (HI) assay used for immunogenicity evaluation of influenza vaccines is considered adequate for the two QIVc studies performed, in line with the recent Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014).

It should be mentioned that HI titres are not a true correlate of protection in the sense that there is not a globally accepted cut-off titre that defines clinical protection. Nonetheless, it has been widely shown that higher HI titres tend to correlate with better protection so HI assay can be used as immunological marker for comparative assessment.

Since QIVc is propagated in a mammalian cell line (MDCK) rather than in embryonated hens' eggs (differently than the conventional influenza vaccines), it is considered adequate that the HI assays had been performed using test antigens propagated in MDCK cells (mammalian cell culture-derived test antigens) rather than antigens from virus grown in eggs. In addition all sera were tested in a single clinical serology laboratory in line with the recommendations of the current CHMP influenza vaccines guideline.

Three validation reports of the HI test were included in the dossier. All validations were carried out according to ICH guidelines Q2A and Q2B, and covered the three seasonal influenza virus types H3N2, H1N1 and B. The parameters assessed were linearity, precision and robustness. All acceptance criteria defined in the analysis validation plan were well achieved, and therefore it is concluded that the HI test was well validated.

Immunogenicity results for QIVc and TIVc presented in this Marketing Authorisation Application (MAA) have also been evaluated according to the former criteria for adults and older adults recommended by CHMP (Note for guidance on harmonisation of requirements for influenza vaccines, CPMP/BWP/214/96, 1997) and/or the current criteria recommended by CBER for paediatric and adult populations. It is considered that the data on fulfilment of these two criteria (CBER and CHMP) are deemed informative, but not critical for the immunogenicity assessment of the vaccine, since the CBER/FDA criteria are not a requirement for approval in the EU, and the CHMP criteria are no longer valid for approval of influenza vaccines. Moreover, it should be noted that no CHMP criteria for paediatric subjects have ever been set.

2.4.5. Conclusions on clinical pharmacology

It is considered that all aspects dealing with clinical pharmacology have been well addressed by the applicant. No questions on clinical Pharmacology were raised to the applicant.

2.5. Clinical efficacy

2.5.1. Dose response study

No dose-finding studies were conducted since the QIVc vaccine compositions and dosing are in line with the antigen dose of other seasonal inactivated non-adjuvanted influenza vaccines already authorised. The dose of QIVc has the same antigen content (15 µg HA per strain in 0.5 ml dose) than the authorised TIVc, but includes an additional 15 µg HA from an influenza B strain that is of the opposite lineage (B/Yamagata versus B/Victoria) as the one contained in TIVc.

Potency of the chosen dose of TIVc, i.e. 15 µg HA per strain in 0.5 ml, has been demonstrated in the clinical efficacy and immunogenicity study V58P13, consistent with immunogenicity results obtained in studies V58P4, V58P9, V58P12, and V58_23. Study V58P13 in subjects 18 to 49 years of age demonstrated that TIVc has an absolute efficacy of 69.5% across all influenza strains and of 83.8% across vaccine-matched influenza strains. Moreover, QIVc complies with the European Pharmacopoeia requirements and contains 15 µg HA per strain and per dose in 0.5 mL volume, which is the standard dose of all intramuscular inactivated non-adjuvanted influenza vaccines used in the EU. In Studies V130_01 and V130_03, QIVc demonstrated non-inferior antibody responses to TIVc. These immune responses are similar to those demonstrated in the efficacy study V58P13 and the other TIVc immunogenicity studies. Data for all TIVc studies, including V58P13, are therefore considered supportive for the dose used in QIVc.

A single dose of QIVc was administered in study V130_01 (which enrolled subjects >18 y) and one or two doses, depending on the vaccination history, in study V130_03 (which enrolled subjects 4 to >18 y). Two doses of vaccine were given to children less than 9 YOA if they had not been previously vaccinated with

a seasonal influenza vaccine. These schedules are endorsed, in line with WHO, CDC and ECDC recommendations and current SmPC of other authorised TIVs.

This approach was considered adequate.

2.5.2. Main studies

The clinical development program of QIVc includes:

- Two phase III pivotal studies to evaluate safety and immunogenicity of QIVc compared with trivalent inactivated vaccines each containing the B lineage strains used in QIVc in adults ≥18 years of age (V130_01) and in paediatrics subjects from 4 to 17 years of age (V130_03);
- One TIVc efficacy study in ≥18 to <50 years-old adults (V58P13);
- Nine TIVc studies to evaluate safety and immunogenicity in adults (V58P1, V58P2, V58P4, V58P4E1, V58P4E2, V58P5, V58P9, V58-23, V58_30OB) and three TIVc studies in children/adolescents (V58P12, V58P15, V58-31).

Study V58_30OB was a post-licensure observational safety study of specific outcomes after Optaflu vaccination among adults in The Health Improvement Network (THIN) database of routine UK primary care records (see section 2.6).

2.5.2.1. Study V130_01

Title of Study: A Phase III, Stratified, Randomized, Double-Blind, Multicenter, NonInferiority Study to Evaluate the Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine and Cell-based Trivalent Subunit Influenza Virus Vaccines in Adults ≥18 Years of Age.

Methods

Study Participants

Approximately 2680 subjects ≥18 years of age were planned to be enrolled in a 1:1 stratified fashion into 2 age cohorts: ≥18 to <65 years of age and ≥65 years of age. Subjects in each age cohort were to be randomized 2:1:1 to receive QIVc, TIV1c, or TIV2c. All subjects were to be evaluated for safety and immunogenicity.

Table 2: Planned and actual number of subjects enrolled

Age Group	Planned				Actual			
	QIVc	TIV1c	TIV2c	Total	QIVc	TIV1c	TIV2c	Total
18 to <65 years	670	335	335	1340	674	334	332	1340
≥65 years	670	335	335	1340	661	342	337	1340
Total	1340	670	670	2680	1335	676	669	2680

There was good agreement between the planned and the actual number of subjects enrolled. Moreover, it is also considered that the total number of subjects enrolled in the study and the stratification by age are appropriate. A significant number of subjects >75 years old were enrolled (~30%, see Table 23 in section 2.5.6).

Subject Characteristics and Main Criteria for Inclusion

Healthy male and female subjects ≥18 years of age at the time of enrolment who has given informed consent can and can comply with study procedures, including follow up, who have not been exposed to influenza (either through expected influenza illness or influenza vaccination) within the past 6 months and who have no contraindications to influenza vaccine were to be enrolled.

Exclusion Criteria

In order to participate in this study, all subjects must meet NONE of the exclusion criteria described.

1. Individuals with body temperature measurement ≥38°C (≥100.4°F) within 3 days prior to vaccination.
2. Individual who (aside from elevated body temperature) otherwise has a chronic or acute illness that, in the opinion of the investigator, would interfere with the subject's safety during study participation.
3. Individual who (aside from elevated body temperature) otherwise has a chronic or acute illness that, in the opinion of the investigator, would interfere with the subject's compliance with study related procedures and/or could interfere with the evaluation of study vaccine.
4. If the individual is female, "of childbearing potential", sexually active, and has not used any of the "acceptable contraceptive methods" for at least 2 months prior to study entry and through Day 60.
5. Individual is a female of childbearing potential with a positive or indeterminate pregnancy test.
6. Individual is a pregnant or breast-feeding female.
7. Individuals who are not able to comprehend or follow all required study procedures for the whole period of the study.
8. Individuals with known history of Guillain-Barré Syndrome.
9. Current alcohol abuse or drug addiction.
10. Individuals with a diagnosis of any bleeding disorder that represents a contraindication to intramuscular vaccination and blood draws.
11. Individuals with a known history of any anaphylaxis, serious vaccine reactions, or hypersensitivity to any of the vaccine components described in the Investigator's Brochure.
12. Individuals with a known anaphylaxis or severe hypersensitivity reaction following exposure to latex.
13. Individual has participated in any clinical trial with another investigational product 30 days prior to first study visit or intent to participate in another clinical study at any time during the conduct of this study. Concomitant participation in an observational study (not involving drugs, vaccines, or medical devices) is acceptable.
14. Individual has received influenza vaccination or has had documented influenza disease within the past 6 months.
15. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or systemic corticosteroid therapy (prednisone or equivalent) at any dose for more than 2

consecutive weeks (14 days) within the past 3 months. Topical, inhaled and intranasal corticosteroids are permitted. Intermittent use (one dose in 30 days) of intra-articular corticosteroids is also permitted.

16. Individual who has received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 12 weeks.
17. Individuals who are employees of the Investigator or study centre, with direct involvement in the proposed study or other studies under the direction of the Investigator or study centre, as well as immediate family members of the employees or the Investigator.

When individuals met all entry criteria except one that relates to transient clinical circumstances (e.g. body temperature elevation or use of an excluded medication), such subjects were to be considered eligible for study enrolment if the associated appropriate window for delay had passed, inclusion/exclusion criteria had been rechecked, and if the subject was confirmed to be eligible. In other words, a subject with an elevated body temperature may have been enrolled if the subject met eligibility criteria and had a body temperature < 38°C (< 100.4°F) for 3 or more days.

A subject who had received the following medication(s)/vaccine may have been enrolled after the specified window had passed and if the subject continued to meet eligibility criteria:

- Influenza vaccine: 6 months after vaccine administration
- Chemotherapy or radiation therapy: 6 months after end of therapy
- Systemic corticosteroids: 3 months since end of continuous use
- Blood/plasma products: 12 weeks since end of therapy

In general, the immunogenicity and safety of QIVc was studied in healthy subjects. Nonetheless, subjects belonging to risk groups for influenza (as people with chronic respiratory diseases, chronic cardiovascular diseases, chronic metabolic disorders and chronic renal and hepatic diseases) were also enrolled in this trial. Furthermore, some immunocompromised subjects were enrolled. Pregnant or breast-feeding women were excluded in this study. The exclusion of pregnant women in the first and unique QIVc adult study is acceptable. However, as reflected in the influenza vaccines guideline (EMA/CHMP/VWP/457259/2014), it is recommended to obtain vaccine effectiveness data in this group. Also, the exclusion of individuals that have received influenza vaccination or have had documented influenza disease within the past 6 months is endorsed, since natural infection would affect the immunogenicity of the vaccine.

In conclusion, the study participants enrolled based on these criteria are considered representative in order to support an age indication from 18 years onwards.

Treatments

The three treatments consist of one tetravalent QIVc and two trivalent (TIVc) vaccines (TIVc1 and TIVc2), each with a different B strain, and these treatments are considered adequate. The active drug substance consisted of 15 µg of HA of each of the three or four viral strains recommended by the WHO and Committee for Medicinal Products for Human Use (CHMP) for the 2013/2014 season in the Northern Hemisphere. For the actual strain formulation of the different vaccines please see Table 18 and Table 19 (summary of main study results, section 2.5.4).

Objectives

The immunogenicity non-inferiority objectives were evaluated based on haemagglutination inhibition (HI) antibody responses three weeks after vaccination, in adults 18 years of age and above.

Primary Immunogenicity Objectives

- To demonstrate non-inferiority of antibody responses of QIVc to comparator TIVc1 in adults 18 years of age and above, as assessed by the ratio of geometric mean titer (GMT) at 3 weeks after vaccination (Day 22) for each of the four vaccine strains.
- To demonstrate non-inferiority of antibody responses of QIVc to comparator TIVc1 three weeks after vaccination (Day 22) in adults 18 years of age and above, as assessed by differences in seroconversion rates for each of the four vaccine strains separately after vaccination.

The study was to be considered a success if both co-primary non-inferiority objectives were achieved.

Key Secondary Immunogenicity Objective

To evaluate the antibody responses to all four influenza vaccine strains after vaccination in two age cohorts, 18 years to < 65 years of age and ≥ 65 years of age, according to the Centre for Biologics Evaluation, Research, and Review (CBER) criteria as defined for the different age-cohorts.

Secondary Immunogenicity Objectives

- To evaluate the antibody responses to all four influenza vaccine strains after vaccination in the two age cohorts: ages 18 years through 60 years and ≥61 years according to the Committee for Medicinal Products for Human Use (CHMP) criteria.
- To demonstrate superiority of antibody responses to the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain) as assessed by GMT ratios and seroconversion rates in adults 18 years and above.
- To demonstrate superiority of antibody responses to the second B strain (B2) in QIVc as compared to TIV1c (containing the B1 strain) as assessed by GMT ratios and seroconversion rates in adults 18 years and above.

Exploratory Immunogenicity Objective

To further characterize the immune response, additional immunogenicity analyses may be conducted using other assays such as microneutralisation (MN), anti-neuraminidase (anti-NA), single radial haemolysis (SRH) assay, and/or HI testing for non-vaccine (heterologous) influenza strains.

Endpoints

For the pooled age cohort (≥18 years of age), as determined by the HI assay, the primary measures of immunogenicity included the following:

1. Geometric mean HI titer (GMT) of all four influenza strains as measured on Day 1, Day 22 (with 95% confidence intervals).
2. Ratio of geometric mean titre (GMT) as calculated at Day 22:
    - A/H1N1: TIV1c/QIVc
    - A/H3N2: TIV1c/QIVc
    - B1: TIV1c/QIVc (non-inferiority comparison), TIV2c/QIVc (superiority comparison)

- B2: TIV2c/QIVc (non-inferiority comparison), TIV1c/QIVc (superiority comparison)

3. Geometric mean ratio (GMR) as calculated for all four influenza strains:
   - Day 22/ Day 1
4. Percentages of subjects achieving seroconversion and HI titre ≥1:40 for all four influenza strains as calculated at Day 1 and Day 22. Seroconversion was defined in subjects seronegative at baseline (i.e. HI titre <1:10 at day 1) as post-vaccination HI titre ≥1:40, and defined in subjects seropositive at baseline (i.e. HI titre ≥1:10 at day 1) as a minimum of a 4-fold increase in post-vaccination HI titre.
5. Differences in percentages of subjects achieving seroconversion as calculated at Day 22:
   - A/H1N1: TIV1c-QIVc
   - A/H3N2: TIV1c-QIVc
   - B1: TIV1c-QIVc (non-inferiority comparison), TIV2c-QIVc (superiority comparison)
   - B2: TIV2c- QIVc (non-inferiority comparison), TIV1c-QIVc (superiority comparison)

Reverse cumulative distribution curves were additionally provided. The comparator vaccines for non-inferiority comparisons by strain are: A/H1N1, A/H3N2, B1: TIV1 and B2: TIV2.

Sample size

The study V58P4 was selected for reference for sample size calculation. Within this study of healthy adult and elderly subjects 18 years of age and above, the standard deviation for the Day 22 geometric mean titres of post-vaccination $\log_{10}$ titre was 0.58 for A/H1N1, 0.47 for A/H3N2, and 0.52 for both B influenza strains. Assuming a true difference of 0 between the vaccine groups and 1-sided alpha of 0.025 for non-inferiority hypothesis testing, the numbers of subjects shown below were required.

Table 3: Sample size estimates for non-inferiority testing of ratio of GMTs in adults and elderly based on V58P4 data

Strain	SD ($\log_{10}$-scale)	NI margin	Effect size (|NI margin|/ SD)	Sample size/group (QIVc/TIV1/2c)	Marginal power
A/H1N1	0.58	$\log_{10}(1.5)$	0.30	1152/576	>99
A/H3N2	0.47	$\log_{10}(1.5)$	0.37	1152/576	>99
Both B Strains	0.52	$\log_{10}(1.5)$	0.34	1152/576	>99

Table 4: Sample size estimates for non-inferiority testing of seroconversion in adults and elderly based on V58P4 data

Strain	% Seroconversion	Sample size/group (QIVc/TIV1/2c)	Marginal power
A/H1N1	62	1152/576	98
A/H3N2	66	1152/576	98
Both B strains	82	1152/576	>99

The sample size for adults 18 years of age and above in this study was calculated to demonstrate that all eight primary hypotheses would be rejected with an overall power of 90% [(0.99^6)*(0.98^2)] and a

1-sided α=0.025, assuming independence. This was considered sufficient to analyse the objectives and endpoints selected for this study.

Randomisation

Approximately 2680 subjects were to be enrolled in a 1:1 stratified fashion into 2 age cohorts: ≥18 years to <65 years of age and ≥65 years of age. After an individual was determined to be eligible for study participation, each age cohort subjects were randomly assigned to the study vaccine in a pre-specified ratio of 2:1:1 to receive either QIVc or TIV1c or TIV2c. The subject was randomized by the investigator via the interactive response technology (IRT) system.

Blinding

This trial was designed as a double blind study. Subjects, investigators, laboratory(ies), and the sponsor were blinded to vaccine assignments. For double-blind studies, the identity of the investigational vaccine was concealed by making it identical in packaging, labelling, schedule of administration, and appearance to the comparator. An emergency unblinding procedure was correctly set up.

Statistical methods

Population for Analysis

1. All Enrolled Set: All screened subjects who provided an informed consent form and demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the trial, and received a subject ID.
2. Exposed Set: All subjects in the enrolled population who received a study vaccination.
3. Full Analysis Set Immunogenicity Set: All subjects in the enrolled population who received the study vaccination and provided immunogenicity data at visit 1 and visit 2.

   Full Analysis Set (FAS) populations were analysed "as randomized" (i.e. according to the vaccine a subject was designated to receive, which could have been different from the vaccine the subject actually received).
4. Per Protocol Population Immunogenicity Set: All subjects in the FAS immunogenicity population who:
   - Correctly receive the vaccine (i.e. receive the vaccine to which the subjects is randomized and at the scheduled time points).
   - Have no major protocol deviations leading to exclusion as defined prior to unblinding/analysis.
   - Are not excluded due to other reasons defined prior to unblinding or analysis.

   Other reasons for exclusion than major protocol deviations were e.g. subjects who withdrew informed consent; subjects with ILI- and RT-PCR-confirmed influenza during the treatment period. Exclusions were considered by objective/time point, i.e. sometimes not all data of a subject but only part of the subject's data was removed from the PPS analysis.

Primary Immunogenicity Objectives

- Non-inferiority objective regarding GMTs (3 weeks after vaccination): The upper bound of the 2-sided 95% confidence interval (CI) for the ratio of GMTs (GMTTIV1c or TIV2c /GMTQIVc) for HI antibody should not exceed the non-inferiority margin of 1.5.
- Non-inferiority objective regarding seroconversion (3 weeks after vaccination): The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody should not exceed the margin of 10%.

The study was to be considered a success if both co-primary non-inferiority objectives were achieved in the pooled age cohort.

Key Secondary Immunogenicity Objective: Immunogenicity according to CBER (3 weeks after vaccination)

The vaccines immunogenicity was evaluated following measurements according to the current CBER criteria (CBER, 2007):

1. for subjects ≥18 to <65 years of age:
    - The lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%.
    - The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titre ≥1:40 should meet or exceed 70%.
2. for subjects ≥65 years of age:
    - The lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30%.
    - The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titre ≥1:40 should meet or exceed 60%.

Secondary Immunogenicity Objectives: Immunogenicity criteria according to CHMP (3 weeks after vaccination)

1. in adults ≥18 to <60 years:
    - The percentage of subjects with seroconversion or significant increase in HI antibody is >40%. *Significant increase* is defined as at least a 4-fold increase in HI titre in subjects seropositive at baseline i.e. HI titre ≥1:10 at day 1.
    - The percentage of subjects achieving an HI titre ≥1:40 is >70%.
    - The GMR is >2.5.
2. in adults ≥61 years of age:
    - The percentage of subjects with seroconversion or significant increase in HI antibody is >30%.
    - The percentage of subjects achieving an HI titre ≥1:40 is >60%.
    - The GMR is >2.0.

All 3 criteria (seroconversion/significant increase, HI antibody titre ≥1:40, and GMR) were assessed for day 22.

Superiority Objectives (3 Weeks After Vaccination)

- The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV1c or TIV2c /GMTQIVc) for HI antibody should not exceed the superiority margin of 1;
- The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – %seroconversion QIVc) for HI antibody should not exceed the margin of 0 points.

Statistical Considerations

The primary objective of non-inferiority of QIVc to TIVc can be translated into 8 co-primary hypotheses:

1. Two hypotheses relating to non-inferiority of HI antibody responses to B1 strain compared between QIVc and TIV1c and of HI antibody responses to B2 strain compared between QIVc and TIV2c, as evaluated by the ratio of GMT.
2. Two hypotheses relating to non-inferiority of HI antibody responses to A/H3N2 and A/H1N1 strains compared between QIVc and TIV1c, as evaluated by the ratio of GMT.
3. Two hypotheses relating to non-inferiority of HI antibody responses to B1 strain compared between QIVc and TIV1c and of HI antibody responses to B2 strain compared between QIVc and TIV2c, as evaluated by difference in seroconversion rate.
4. Two hypotheses relating to non-inferiority of HI antibody responses to A/H3N2 and A/H1N1 strains compared between QIVc and TIV1c, as evaluated by difference in seroconversion rate.

The study was to be declared successful if all primary objectives, i.e. both of the co-primary objectives (associated with 8 hypotheses) were met, so the overall null hypothesis was to be rejected if all 8 single null hypotheses were rejected at 1-sided alpha 0.025. The analysis population for non-inferiority testing was based on the PPS.

Results

Participant flow

A total of 2680 subjects were enrolled into the study. Of these, 1335 subjects in QIVc group, 676 subjects in TIV1c group and 669 subjects in TIV2c group. Of the 2680 enrolled subjects, 2585 (96.5%) completed the study. A total of 95 (3.5%) subjects were prematurely withdrawn from the study (equally spread across treatment groups). Across the groups, the most common reason for premature withdrawal was lost to follow-up by 48 (1.8%) subjects. The reasons for withdrawal were unrelated to the study vaccination and were similar in the QIVc and the two TIVc groups in both adults and elderly. There is no indication of selective discontinuation for safety reasons.

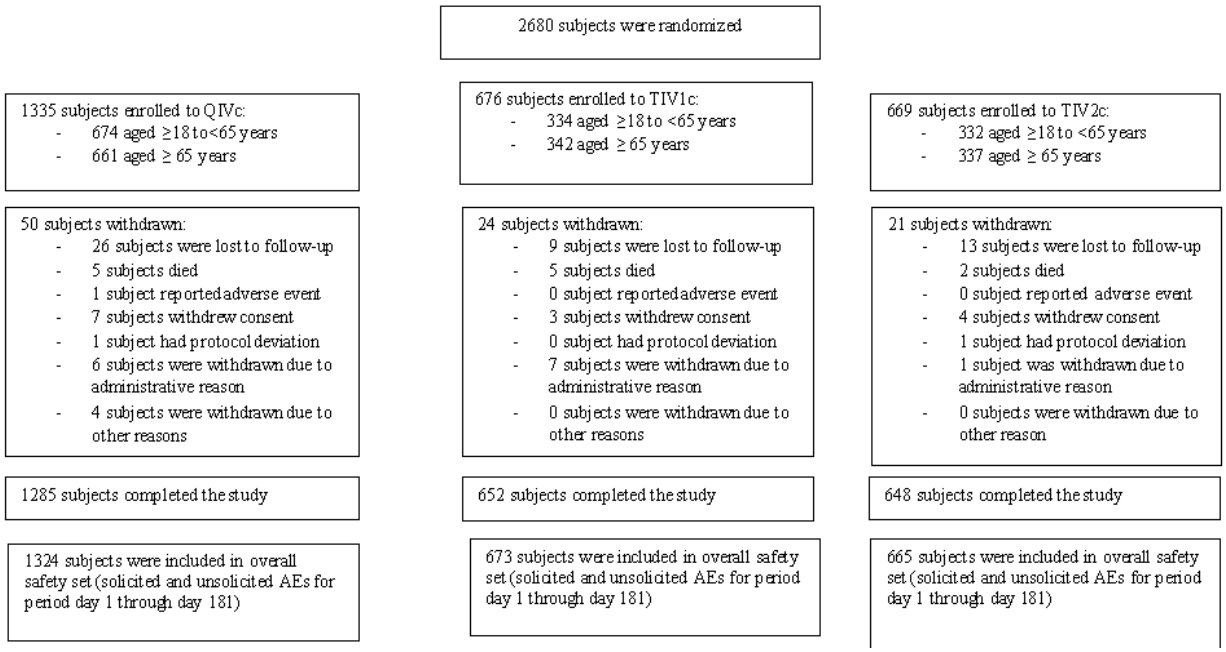

Figure 1: Subjects disposition flowchart

Recruitment

Study V130_01 was conducted in 40 centres in USA. The first subject entered the study on 14 November 2013 and the last subject completed the last visit on 11 July 2014.

Conduct of the study

All protocol deviations were classified as major or minor, and all the major deviations impacting immunogenicity assessments led to exclusion from the PPS. A total of 143 (5.3%) subjects were defined as having major protocol deviations in the study. The most common major protocol deviation across all the groups was noncompliance with blood draw schedules in 99 (3.7%) subjects. These deviations are considered not to have influenced the outcome of the study.

Baseline data

Subjects 18 to <65 Years of Age (PPS)

The mean age (±SD) was 43.0 (±12.82), 42.3 (±12.78), and 42.0 (±12.80) years in the QIVc, TIV1c, and TIV2c groups, respectively. The proportion of female subjects was higher across all vaccine groups and was higher in the TIV1c and TIV2c groups (59.5% and 62.0%, respectively) than in the QIVc group (54.4%). The majority of subjects (64.5% to 70.3% across vaccine groups) were Caucasian (not of Hispanic or Latino ethnicity).

Subjects ≥65 Years of Age (PPS)

The mean age (±SD) was 72.3 (±5.49), 72.1 (±5.50), and 72.2 (±5.49) years in the QIVc, TIV1c, and TIV2c groups, respectively. The proportion of female subjects was higher and comparable across vaccine groups (55.9%, 57.1% and 57.3% for QIVc, TIV1c and TIV2c, respectively). The majority of subjects (87.8% to 88.0% across vaccine groups) were Caucasian (not of Hispanic or Latino ethnicity).

The number of subjects per age groups is shown in the table below.

Table 5: Number (%) of subjects

	Number (%) of Subjects								
	18 to < 65 Years of Age			≥ 65 Years of Age			≥ 18 Years of Age		
	QIVc N = 629	TIV1c N = 309	TIV2c N = 316	QIVc N = 621	TIV1c N = 326	TIV2c N = 323	QIVc N = 1250	TIV1c N = 635	TIV2c N = 639
Influenza Vaccination Within Past 12 Months									
Yes	123 (19.6)	67 (21.7)	66 (20.9)	186 (30.0)	95 (29.1)	94 (29.1)	309 (24.7)	162 (25.5)	160 (25.0)

#

Subjects >75 Years of Age (PPS)

As would be expected in this age group, there were more females (51.3% to 55.4% across vaccine groups) than males. Most subjects were Caucasian (89.3% to 95.1% across vaccine groups). The number of subjects >75YOA in the immunogenicity PP population were 150 for QIVc, 83 for TIV1c, 82 for TIV2c.

The percentage of subjects who received previous influenza vaccination was similar among three groups. As expected from current use recommendations of the influenza vaccine (recommended annually for those older than 60-65 years of age), the percentage of subjects that received a previous influenza vaccination within the previous 12 months was higher in >65 years of age (around 30%) than in those 18 to 65 years old (20%).

Medical history in study V130_01 was coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 system organ classes (SOCs) and preferred terms (PTs). Medical histories were typical for the age groups and balanced between the vaccine groups. The rates of pre-existing conditions were generally high, as expected for this age population, and thus this is appropriate considering that they represent the primary candidates for annual influenza vaccination.

Numbers analysed

The total number of subjects enrolled, the FAS and the PPS population for QIVc, TIV1c and TIV2c groups are presented by age group in the Table below.

Table 6: Overview of analysis sets in subjects ≥18YOA as randomised, study V130_01

	Number (%) of Subjects								
	18 to < 65 Years of Age			≥ 65 Years of Age			≥ 18 Years of Age		
	QIVc	TIV1c	TIV2c	QIVc	TIV1c	TIV2c	QIVc	TIV1c	TIV2c
All Enrolled	674 (100.0)	334 (100.0)	332 (100.0)	661 (100.0)	342 (100.0)	337 (100.0)	1335 (100.0)	676 (100.0)	669 (100.0)
FAS	661 (98.1)	328 (98.2)	326 (98.2)	650 (98.3)	336 (98.2)	332[a] (98.5)	1311 (98.2)	664 (98.2)	658[b] (98.4)
PPS	629 (93.3)	309 (92.5)	316 (95.2)	621 (93.9)	326 (95.3)	323 (95.8)	1250 (93.6)	635 (93.9)	639[c] (95.5)

Sources: section 5.3.5.1, CSR V130_01 Table 14.1.1.1 and Table 14.1.1.1.1.4.
Abbreviations: FAS = full analysis set; PPS = per protocol set; QIVc = cell-based quadrivalent influenza vaccine; TIVc = cell-based trivalent influenza vaccine.
[a] 331 (98.2) for A/H1N1 and B1.
[b] 657 (98.2) for A/H1N1 and B1.
[c] 638 (95.4) for A/H1N1 and B1.

Outcomes

Primary Objective

The primary non-inferiority objective was assessed by the ratio of GMTs and difference in seroconversion rates in subjects ≥18 years of age. Overall, at day 22 (3 weeks after the vaccination), non-inferiority criteria as assessed by the ratio of GMTs and differences in seroconversion rates was achieved for all 4 influenza strains, indicating non-inferiority of the QIVc vaccine over the TIV1c vaccine for the 3 influenza strains (A/H1N1, A/H3N2 and B1) and over the TIV2c vaccine for B2 influenza strain (Table 7).

- Geometric mean titres: At day 22 (3 weeks after the vaccination), for all 4 strains, the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV1c or TIV2c /GMT QIVc) for HI antibody remained within the non-inferiority margin of 1.5 (1.1 for A/H1N1, 1.1 for A/H3N2, 1.0 for B1 and 1.0 for B2).
- Seroconversion: At day 22 (3 weeks after the vaccination), for all 4 influenza strains, the upper bound of the 2-sided 95% CI on the difference between the seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody did remained within the non-inferiority margin of 10% (4.2% for A/H1N1, 1.9% for A/H3N2, 2.8% for B1 and 0.2% for B2.

Table 7: Non-inferiority of QIVc relative to TIVc in adults 18 years of age and above – Per Protocol Analysis Set

		QIVc N = 1250	**TIV1c/TIV2c[a] N = 635/N =639**	**Vaccine Group Ratio (95% CI)**	**Vaccine Group Difference (95% CI)**
A/H1N1	GMT (95% CI)	302.8 (281.8-325.5)	298.9 (270.3-330.5)	1.0 (0.9-**1.1**)	-
	Seroconversion Rate[b] (95% CI)	49.2% (46.4-52.0)	48.7% (44.7-52.6)	-	-0.5% (-5.3-**4.2**)
A/H3N2	GMT (95% CI)	372.3 (349.2-396.9)	378.4 (345.1-414.8)	1.0 (0.9-**1.1**)	-
	Seroconversion Rate[b] (95% CI)	38.3% (35.6-41.1)	35.6% (31.9-39.5)	-	-2.7% (-7.2-**1.9**)
B1	GMT (95% CI)	133.2 (125.3-141.7)	115.6 (106.4-125.6)	0.9 (0.8-**1.0**)	-
	Seroconversion Rate[b] (95% CI)	36.6% (33.9-39.3)	34.8% (31.1-38.7)	-	-1.8% (-6.2-**2.8**)
B2	GMT (95% CI)	177.2 (167.6-187.5)	164.0 (151.4-177.7)	0.9 (0.9-**1.0**)	-
	Seroconversion Rate[b] (95% CI)	39.8% (37.0-42.5)	35.4% (31.7-39.2)	-	-4.4% (-8.9-**0.2**)

Abbreviations: GMT = geometric mean titer; CI = confidence interval.
[a] The comparator vaccine for non-inferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 it is TIV2c.
[b] Seroconversion rate = percentage of subjects with either a pre-vaccination HI titre <1:10 and post-vaccination HI titre ≥1:40 or with a pre-vaccination HI titre ≥1:10 and a minimum 4-fold increase in post-vaccination HI antibody titre.

The primary immunogenicity analysis (non-inferiority) was performed using the PPS analysis population which is a more conservative approach for non-inferiority studies consistent with ICH E9. The immunogenicity analysis was also performed using the Full Analysis Set (FAS) at the time of the initial analysis. The primary endpoints - GMT ratio and seroconversion rate- analysed for the PPS population and the FAS population showed consistent results.

Key Secondary Immunogenicity Objective

Assessment of vaccine immunogenicity based on CBER criteria in subjects ≥18 to <65 years of age and ≥65 years of age.

- ≥18 to <65 years of age: At day 22, both CBER immunogenicity criteria for seroconversion and HI titre ≥1:40 were met for A/H1N1 (QIVc SCR 63.1%, HI >40: 98.5%), A/H3N2 (QIVc SCR 49.2%, HI >40 98.6%), B1 (QIVc SCR 52.1%, HI >40: 95.6%) and B2 (QIVc SCR 52.8%, HI >40: 99.15) influenza strains by the QIVc and the TIV1c/TIV2c vaccines.

- ≥65 years of age: At day 22 (3 weeks after the vaccination), both CBER immunogenicity criteria for seroconversion and HI titre ≥1:40 were met for A/H1N1 (QIVc SCR 34.5%, HI >40: 94.3%) influenza strain by the QIVc and the TIV1c/TIV2c vaccines. For A/H3N2 (QIVc SCR 27.2%, HI >40: 98.3%), B1 (QIVc SCR 20.9%, HI >40: 62.2%) and B2 (QIVc SCR 26.3%, HI >40: 98.8%) influenza strains while the CBER immunogenicity criteria for HI titre ≥1:40 was met, the criteria for seroconversion was not met by the QIVc or the TIV1c/TIV2c vaccines.

Secondary Immunogenicity Objectives

1. Assessment of vaccine immunogenicity based on CHMP criteria in subjects ≥18 to <60 years of age and ≥61 years of age:

    - ≥18 to <60 years of age: At day 22 (3 weeks after the vaccination), all 3 CHMP immunogenicity criteria for seroconversion, HI titre ≥1:40 and GMR were met for A/H1N1, A/H3N2, B1 and B2 influenza strains by the QIVc and the TIV1c/TIV2c vaccines. Percentages observed were similar to those seen against the CBER criteria.

    - ≥61 years of age: At day 22 (3 weeks after the vaccination), all 3 CHMP immunogenicity criteria for seroconversion, HI titre ≥1:40 and GMR were met for A/H1N1 influenza strain by the QIVc and the TIV1c/TIV2c vaccines. Against A/H3N2, and B2 influenza strains 2 CHMP criteria for HI titre ≥1:40 and GMR were met by the QIVc and the TIV1c/TIV2c vaccines. Against the B1 influenza strain the QIVc vaccine met 2 CHMP criteria for HI titre ≥1:40 and GMR, whereas the TIV1c/TIV2c vaccine met 1 CHMP criteria for HI titre ≥1:40. Percentages observed were similar to those seen against the CBER criteria.

2. To demonstrate superiority of antibody responses to the first influenza B strain (B1) in QIVc as compared to TIV2c (containing the influenza B2 strain) and the second influenza B strain (B2) in QIVc as compared to TIV1c (containing the influenza B1 strain) as assessed by GMT ratios and differences in seroconversion rates in subjects ≥18 years of age at day 22 (3 weeks after the vaccination):

    - Geometric Mean Titres: At day 22, the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT_{TIV2c} [76.3] /GMT_{QIVc} [177.1]) for HI antibody did not exceed 1, thereby establishing superiority (0.5, 2-sided 95% CI: 0.5-0.5).

    - Seroconversion: At day 22, the upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV2c [18%]– %seroconversion QIVc[39.7%]) for HI antibody did not exceed the margin of 0 points, thereby establishing superiority of QIVc over TIV2c for B1 influenza strain (-21.7%, 2 sided 95% CI:- 25.5%, -17.7%).

    - similar results were observed vs. TIV1c.

Exploratory Immunogenicity Objectives: these were not conducted in light of the fact that the primary research questions were addressed satisfactorily.

Additional post-hoc analyses

The applicant performed analyses in study population subsets according to age, sex/gender, race/ethnicity, baseline immune status, previous vaccination status, and history of medical conditions than might increase the risk for complications from influenza.

Immunogenicity Results Stratified by age

In the PPS of the QIVc, TIV1c and TIV2c groups, 629, 309 and 316 subjects, respectively, were 18 to <65 years of age and 621, 326 and 323 subjects, respectively, were ≥65 years of age at enrolment. Demographic and other baseline characteristics were balanced between these 2 age groups.

Within both age subgroups, GMTs, GMRs and seroconversion rates were comparable between the QIVc and TIV1c/TIV2c groups for all 4 strains (i.e. overlapping 95% CIs). GMTs, GMRs and seroconversion rates were higher in the 18 to <65 years of age group when compared with the ≥65 years of age group for all 4 strains.

Although the study was not formally powered to evaluate non-inferiority of QIVc to TIVc in the subgroups, the data indicate that both in subjects 18 to < 65 years of age and in subjects ≥ 65 years of age, at 3 weeks after the last vaccination, criteria for non-inferiority were met for all 4 strains.

Table 8: Immunogenicity results at 3 weeks after vaccination in subjects ≥18YOA, by age, HI assay (PPS), study V130_01

		18 to < 65 Years of Age				≥ 65 Years of Age			
	Day 22	QIVc N = 629	TIV1c/TIV2c[a] N = 309/N = 316	Vaccine Group Ratio[b] (95% CI)	Vaccine Group Difference[c] (95% CI)	QIVc N = 621	TIV1c/TIV2c[a] N = 326/N = 323	Vaccine Group Ratio[b] (95% CI)	Vaccine Group Difference[c] (95% CI)
A/H1N1	GMT (95% CI)	472.2 (429.4, 519.2)	432.2 (374.7, 498.5)	0..9 (0.8, **1.1**)	NA	193.1 (175.3, 212.8)	210.7 (184.8, 240.2)	1.1 (0.9, **1.2**)	NA
	Seroconversion Rate[d] (95% CI)	63.3% (59.4, 67.1)	60.2% (54.5, 65.7)	NA	-3.1% (-9.7, **3.4**)	34.9% (31.2, 38.8)	37.7% (32.4, 43.2)	NA	2.8% (-3.5, **9.2**)
A/H3N2	GMT (95% CI)	414.1 (379.4, 452.0)	410.5 (361.5, 466.0)	1.0 (0.9, **1.1**)	NA	334.2 (304.5, 366.9)	350.3 (306.7, 400.0)	1.0 (0.9, **1.1**)	NA
	Seroconversion Rate[d] (95% CI)	49.1% (45.2, 53.1)	46.6% (40.9, 52.3)	NA	-2.5 (-9.2, **4.2**)	27.4% (23.9, 31.1)	25.2% (20.5, 30.2)	NA	-2.2% (-7.9, **3.7**)
B1	GMT (95% CI)	186.6 (171.0, 203.5)	167.7 (149.5, 188.1)	0.9 (0.8, **1.0**)	NA	94.7 (87.5, 102.4)	81.3 (73.1, 90.4)	0.9 (0.8, **1.0**)	NA
	Seroconversion Rate[d] (95% CI)	52.0% (48.0, 56.0)	50.5% (44.8, 56.2)	NA	-1.5% (-8.2, **5.2**)	20.9% (17.8, 24.3)	19.9% (15.7, 24.7)	NA	-1.0% (-6.2, **4.5**)
B2	GMT (95% CI)	225.9 (208.9, 244.3)	198.4 (176.9, 222.5)	0.9 (0.8, **1.0**)	NA	138.6 (128.5, 149.5)	136.2 (122.2, 151.9)	1.0 (0.9, **1.1**)	NA
	Seroconversion Rated (95% CI)	52.5% (48.5, 56.4)	50.3% (44.7, 56.0)	NA	-2.2% (-8.8, **4.5**)	26.9% (23.4, 30.6)	20.7% (16.5, 25.6)	NA	-6.2% (-11.6, **-0.4**)

Abbreviations: HI = hemagglutination inhibition; PPS = per protocol set; GMT = geometric mean titer; CI = confidence interval; NA = not applicable.
[a] The comparator vaccine for noninferiority comparisons for A/H1N1, A/H3N2 and B1 is TIV1c, for B2 it is TIV2c.
[b] $GMT_{TIV1c/TIV2c}/GMT_{QIVc}$.
[c] Seroconversion rate TIV1c/TIV2c – seroconversion rate QIVc.
[d] Seroconversion rate = percentage of subjects with either a prevaccination HI titer < 1:10 and postvaccination HI titer ≥ 1:40 or with a prevaccination HI titer ≥ 1:10 and a minimum 4-fold increase in postvaccination HI antibody titer.
Bold = Noninferiority criterion met. The upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT_{TIV1c} or $_{TIV2c}$ /GMT_{QIVc}) for HI antibody should not exceed the noninferiority margin of 1.5. The upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody should not exceed the margin of 10%. Please note that study V130_01 was not formally powered to assess noninferiority in the subgroups presented in this table.

Immunogenicity Results Stratified by Sex and Race/Ethnicity

In the PPS of all 3 vaccine groups, slightly more female (QIVc: 55.1%, TIV1c: 58.3%, TIV2c: 59.6%) than male subjects were included. The applicant presented immunogenicity results at 3 weeks after the last vaccination, stratified by sex, for subjects ≥ 18 years of age: percentages of subjects achieving HI titre ≥ 1:40 and seroconversion rates were comparable between female and male subjects for all vaccines.

Across PPS vaccine groups, similar percentages of subjects ≥ 18 years of age were Caucasian, Black and Hispanic. The majority of subjects was Caucasian (QIVc: 76.1%, TIV1c: 77.3%, TIV2c: 79.2%), followed by Black (QIVc: 13.0%, TIV1c: 11.5%, TIV2c: 11.4%) and Hispanic (QIVc: 9.0%, TIV1c: 8.5%, TIV2c: 7.8%). Group sizes for American Indian, Asian, Native Hawaiian and Other were too small to obtain meaningful results.

Percentages of subjects achieving HI titre ≥ 1:40 were comparable between Caucasian, Black and Hispanic subjects for all 4 strains in all vaccine groups. GMTs and seroconversion rates, however, were generally lower in the Caucasian populations for all strains in all vaccine groups when compared to Black and Hispanic subjects. The clinical implication, if any, of these differences is unknown but the results should be interpreted with caution due to the large difference in sample size for Black (QIVc: 163, TIV1c and TIV2c: 73) and Hispanic subjects (QIVc: 113, TIV1c: 54, TIV2c: 50) when compared to Caucasian subjects (QIVc: 951, TIV1c: 491, TIV2c: 506), as well as the difference in distribution of Black, Hispanic and Caucasian subjects within the different age subgroups (18 to < 65 and ≥ 65 years of age, Table 20 section 2.5.5). Other studies have also observed a higher immune response in terms of HI titres in the Black and African-Americans as compared to Caucasian subjects. The biological mechanism behind this observation is unknown. Nonetheless, in terms of vaccine efficacy in trial V58P13 a VE of 83.8% was demonstrated. This trial enrolled mostly Caucasian subjects (84%) and only 7% of Black or African Americans. Thus, this estimate of VE can be considered to be that of Caucasian subjects and this represents an adequate VE. Obviously the higher immunogenicity response observed for Black and African-Americans would therefore not represent a problem in terms of VE.

Immunogenicity Results Stratified by Baseline Immune Status (i.e. baseline HI titre < 1:10 or ≥ 1:10)

In the PPS for QIVc and TIV1c/TIV2c, the majority of subjects were seropositive for all 4 strains at baseline (Day 1, before vaccination). For the A/H1N1 strain 86.0% and 85.5% of subjects in the QIVc and TIV1c groups, respectively, were seropositive; for the A/H3N2 strain, 93.8% and 93.7% of subjects in the QIVc and TIV1c groups, respectively, were seropositive; for the B1 strain 94.2% and 95.3% of subjects in the QIVc and TIV1c groups, respectively, were seropositive; and for the B2 strain 97.2% and 96.9% of subjects in the QIVc and TIV2c group were seropositive.

In the QIVc and TIV1c/TIV2c groups, subjects seronegative at baseline had lower point-estimate GMTs and percentages of subjects achieving HI titre ≥ 1:40 for all 4 strains when compared to subjects seropositive at baseline. Seroconversion rates were higher in subjects seronegative at baseline compared to subjects seropositive at baseline for all 4 strains in the QIVc and TIV1c/TIV2c groups. Although the percentage of subjects with post vaccination HI titres ≥1:40 were higher in seropositive subjects at baseline, they were still well above CBER and CHMP thresholds regardless of baseline serostatus. The results of the baseline HI titre analyses are consistent with past influenza exposure in the elderly population as enrolled in study V130_01.

2.5.2.2. Study V130_03

Title of Study: A Phase III, Stratified, Randomized, Double-Blind, Multicentre, Non-Inferiority Study to Evaluate Safety and Immunogenicity of Cell-Based Quadrivalent Subunit Influenza Virus Vaccine and Cell-Based Trivalent Subunit Influenza Virus Vaccines in Subjects Ages ≥4 Years to <18 Years

Methods

Study Participants

Approximately 2352 subjects ≥4 to <18 years of age (2000 evaluable subjects, assuming a dropout rate of 15%) were to be enrolled in a 1:1 stratified fashion into 2 age cohorts: ≥4 years to <9 years of age and ≥9 years to <18 years of age. Subjects between ≥4 to <9 years of age were to be further stratified by previous influenza vaccine status as "previously vaccinated" and "not previously vaccinated", and within each treatment arm, at least 30% and not more than 50% subjects who have been "previously vaccinated" against influenza were to be enrolled. Subjects were to be randomized at an approximately 2:1:1 ratio to receive QIVc, TIV1c, or TIV2c vaccine.

Table 9: Planned and actual number of subjects enrolled

Age Cohort	≥4 to <9 years				≥9 to <18 years		≥4 to <18 years	
Vaccine	Not Previously Vaccinated" Subjects		Previously Vaccinated" Subjects					
	Planned	Actual	Planned	Actual	Planned	Actual	Planned	Actual
QIVc	~412 to 294	340	~176 to 294	235	588	584	1176	1159
TIV1c	~206 to 147	173	~88 to 147	120	294	300	588	593
TIV2c	~206 to 147	181	~88 to 147	113	294	287	588	581
Total	~ 823 to 588	694	~353 to 588	468	1176	1171	2352	2333

The definitions of "previously vaccinated" and "not previously vaccinated" subjects for the purposes of this study are as follows:

3. "Previously Vaccinated" Subjects:
    - Any child 9 years of age and older.
    - Any child under the age of 9 years who has received 2 or more doses of seasonal influenza vaccine since July 1, 2010.
4. "Not Previously Vaccinated" Subjects:
    - Any child under the age of 9 years who does not meet the conditions for "previously vaccinated" (including fewer than 2 doses given since 2010 or receipt of exclusively nonseasonal [pandemic] influenza vaccines).
    - Any child under the age of 9 years with unknown influenza vaccination history.

Inclusion and exclusion criteria were the same as study V130_01.

Treatments

Treatments were the same as for study V130_01. For vaccines formulations see Table 18 Summary of results in section 2.5.4.

After randomization on day 1, all subjects were to receive an approximate dose of 0.5 mL of study vaccine to which they were assigned, administered IM in the deltoid muscle, preferably of the non-dominant arm. For those subjects who were "not previously vaccinated" a second vaccination was to be administered on day 29.

Objectives

Immunogenicity Objectives

The immunogenicity objectives will be evaluated based on haemagglutination inhibition (HI) antibody responses in the pooled age group (≥4 to <18 years of age) three (3) weeks after last vaccination.

Primary and secondary immunogenicity objectives are the same as for study V130_01.

Endpoints

Endpoints were the same as for study V130_01, with the difference that for study V130_03 all measurements were taken at Day 22 for previously vaccinated subjects and at Day 50 for not previously vaccinated subjects. Hence the ratios were calculated as Day 22/Day 1 and Day 50/Day 1 respectively.

Sample size

The study V58P12 was selected for reference. Within this study of children 3 to 8 years of age, the standard deviation of the geometric mean titres at 3 weeks after last vaccination (Day 50) was 0.71 for B strain, 0.56 for A/H1N1, and was 0.59 for A/H3N2, respectively. Considering a true difference of 0 between the vaccine groups and using a two group t-test with 1-sided alpha of 0.025 and with unbalance design using a ratio of 2:1 the numbers of subjects shown in Table 10 are required.

Table 10: Sample size estimates for non-inferiority testing of GMT ratios in subjects ≥4 to <18 YOA

Strain	SD (log10-scale)	NI margin	Effect size (|NI margin|/SD)	Sample size/group (QIVc/TIV1/2c)	Marginal power
A/H1N1	0,56	$\log_{10}(1.5)$	0.31	1000/500	>99
A/H3N2	0,59	$\log_{10}(1.5)$	0.3	1000/500	>99
Both B Strains	0,71	$\log_{10}(1.5)$	0.25	1000/500	>99

Sample size estimates based on seroconversion rate 3 weeks after last vaccination (day 50) in children 3 to 8 years of age from Study V58P12 are shown in Table 11.

Table 11: Sample size estimates for non-inferiority testing of seroconversion in subjects ≥4 to <18 YOA

Strain	% Seroconversion	Sample size/group (QIVc/TIV1/2c)	Marginal power
A/H1N1	96	1000/500	>99
A/H3N2	80	1000/500	>99
Both B Strains	58	1000/500	96

The sample size for subjects ≥4 to <18 years of age was calculated to demonstrate that all 8 primary hypotheses (NI in terms of GMT and seroconversion) will be rejected with an overall power of approximately 86% and a 1-sided α =0.025, assuming independence. Assuming a drop-out rate and exclusions from PPS of approximately 15%, 1176 subjects in QIVc arm and 588 in each of the TIV1c and TIV2c arm were to be enrolled.

Randomisation

Enrolled subjects were first split into age cohorts based on age at time of enrolment (≥4 to <9 years of age and ≥9 to <18 years of age). Within the ≥4 to <9 years of age cohort, subjects were further stratified as "previously vaccinated" and "not previously vaccinated" based on the definition of "previously vaccinated" and "not previously vaccinated" subjects for the purposes of this study.

In each age cohort subjects were randomly assigned to the study vaccine in a prespecified ratio of 2:1:1 to receive either QIVc or TIV1c or TIV2c by an IRT system.

Blinding

Blinding was the same as for Study V130_01.

Statistical methods

Methods and study populations were the same as for study V130_01.

Subgroups

Analyses of GMT, GMRs, seroconversion and HI titre ≥1:40 were repeated and stratified (using PPS):

- by baseline titre (e.g., for influenza HI titre ≤1:10 vs. >1:10),
- age groups: ≥4 to <9, ≥9 to <18 years of age and ≥4 to <6 years of age, ≥6 to <9 years of age, and ≥9 to <18 years of age;
- by centre
- by sex
- by race/ethnicity
- by previous vaccination status (i.e. day 22 and day 50 results not pooled).

Results

Participant flow

A total of 2333 subjects were enrolled into the study:

- 1159 subjects in the QIVc group
- 593 subjects in the TIV1c group
- 581 subjects in the TIV2c group

Of the 2333 enrolled subjects 2196 (94%) completed the study. A total of 137 (6%) subjects were prematurely withdrawn from the study. Across the groups, the most common reason for premature withdrawal was lost to follow-up by 94 (4%) subjects.

Table 12: Summary of Study Termination– All Enrolled Set

Vaccine Group	QIVc	TIV1c	TIV2c
Enrolled (N)	1159	593	581
Exposed	1159 (100%)	593 (100%)	580 (100%)
Completed	1091 (94%)	560 (94%)	545 (94%)
Premature Withdrawals	68 (6%)	33 (6%)	36 (6%)
Adverse Event	0	1 (<1%)	0
Withdrawal by subject	13 (1%)	7 (1%)	8 (1%)
Lost to follow-up	46 (4%)	22 (4%)	26 (4%)
Administrative reasons	2 (<1%)	0	0
Other	7 (<1%)	3 (<1%)	2 (<1%)

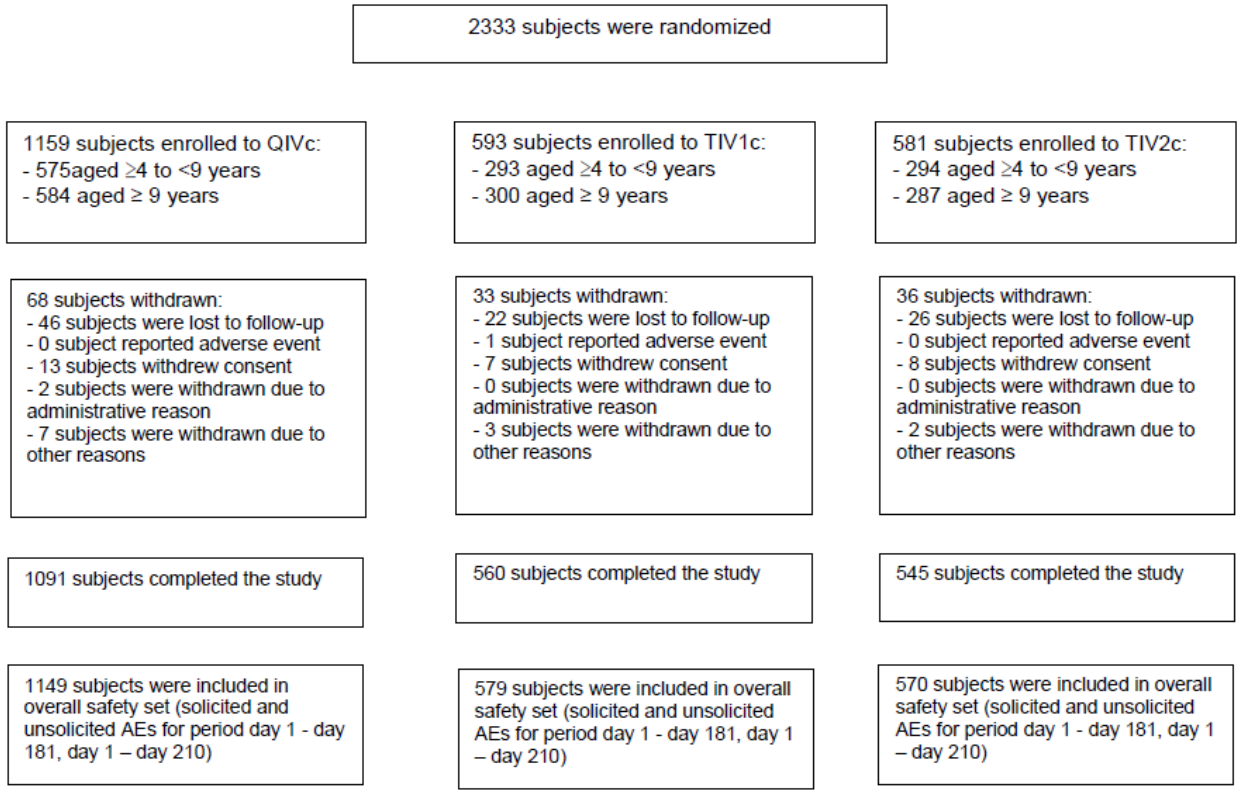

Figure 2: V130_03 subject disposition chart

Recruitment/Conduct of the study

Date of first enrolment: 07 November 2013 - Date of last visit: 19 August 2014. The study was conducted in the USA.

All protocol deviations were classified as major or minor, all major deviations impacting immunogenicity assessments led to exclusion from the PPS. A total of 295 (13%) subjects were defined as having major protocol deviations in the study. The most common major protocol deviation across all the groups was noncompliance with blood draw schedules in 132 (6%) subjects. Other common major protocol deviation were unavailability of serological results in 74 (3%) subjects, noncompliance with study vaccination schedule in 62 (3%) subjects, missing second vaccination in 35 (2%) subjects and no blood draw at day 50 in 17 (<1%) subjects and no blood draw at day 22 in 6 (<1%) subjects.

Overall the percentage of subjects with a major protocol deviation was small, and it is considered that this did not influence the outcome of the study.

Baseline data

Overall the demographic characteristics were comparable between study groups. This balance was maintained in the whole population and also in the two age subgroups: 4 to <9 y and 9 to <18 y. Most of the participants were of Caucasian origin. A good balance between the three treatments groups was observed regarding previous vaccination status for subjects younger than 9 years of age. There was a high level of subjects previously vaccinated (69 to 71 %, 100% in the 9-18 years group, 45 % in the 4-8 years group). Medical histories were typical for the age group and balanced between the vaccine groups.

Table 13: Demographic and baseline characteristics – All enrolled set

Vaccine Group	QIVc	TIV1c	TIV2c
	N=1159	N=593	N=581
Age (years)	9.5±3.8	9.5±3.8	9.3±3.7
Sex			
Male	603 (52%)	309 (52%)	297 (51%)
Female	556 (48%)	284 (48%)	284 (49%)
Height (cm)±SD	139.4±22.14	139.3±21.26 N=592	139.0±21.39 N=578
Weight (kg) ±SD	40.82±21.95	40.64±20.69 N=592	40.40±20.97 N=578
Body Mass Index (kg/m^2) ±SD	19.6±5.34	19.6±5.26 N=592	19.6±5.76 N=578
Race/Ethnic:			
Asian	7 (<1%)	2 (<1%)	2 (<1%)
American Indian	4 (<1%)	4 (<1%)	6 (1%)
Black	261 (23%)	131 (22%)	118 (20%)
Caucasian	614 (53%)	321 (54%)	308 (53%)
Hispanic	227 (20%)	114 (19%)	122 (21%)
Native Hawaiian	5 (<1%)	1 (<1%)	5 (<1%)
Other	41 (4%)	20 (3%)	20 (3%)
Met entry criteria			
Yes	1158 (100%)	593 (100%)	580 (100%)
Previous influenza Vaccination			
Yes	819 (71%)	420 (71%)	400 (69%)

Numbers analysed

A total of 2333 subjects were enrolled into the study. Of these, 1159 subjects were enrolled in QIVc group, 593 subjects in TIV1c group and 581 subjects in TIV2c group.

FAS included 2236 (96% of the enrolled population). Of these, 210 subjects were excluded from the PPS. PPS was composed of 2026 (87% of the enrolled population. In total 68 (6%) subjects in the QIVc group, 33 (6%) subjects in the TIV1c group and 36 (6%) subjects in the TIV2c group were withdrawn from the study, the majority were lost to follow-up (4% of subjects in all vaccine groups).

Table 14: Overview of data sets analysed – as randomised

Vaccine Group	QIVc	TIV1c	TIV2c
Enrolled	1159	593	581
FAS	1113 (96%)	566 (95%)	557 (96%)
A/H1N1	1113 (96%)	566 (95%)	557 (96%)
A/H3N2	1112 (96%)	566 (95%)	557 (96%)
B1	1112 (96%)	566 (95%)	557 (96%)
B2	1108 (96%)	563 (95%)	556 (96%)
PPS	1014 (87%)	510 (86%)	502 (86%)
A/H1N1	1014 (87%)	510 (86%)	502 (86%)
A/H3N2	1013 (87%)	510 (86%)	502 (86%)
B1	1013 (87%)	510 (86%)	502 (86%)
B2	1009 (87%)	508 (86%)	501 (86%)

As shown in Table 14 above, in the three treatment groups a low percentage of the enrolled subjects were excluded from the FAS population and a relatively higher number of subjects from the PPS population. Importantly the percentages were similar across the three treatment groups and after analysing the

excluded subject there is no indication that a bias has been introduced in the two populations (FAS and PPS) as compared to the "all enrolled" set.

Outcomes

Primary Objective: non-inferiority of QIVc vs. TIVc assessed by the ratio of GMTs and difference in seroconversion rates in subjects ≥4 to <18 years of age.

Overall, at day 22 or day 50 (3 weeks after the last vaccination), non-inferiority criteria as assessed by the ratio of GMTs and differences in seroconversion rates was achieved for all 4 strains, indicating non-inferiority of the QIVc vaccine over the TIV1c/TIV2c vaccines.

Geometric mean titres

At day 22 or day 50 (3 weeks after the last vaccination), for all 4 influenza strains, the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMTTIV1c or TIV2c /GMTQIVc) for HI antibody remained within the non-inferiority margin of 1.5 (1.14 for A/H1N1, 1.14 for A/H3N2, 1.1 for B1 and 1.14 for B2 influenza strains).

Seroconversions

At day 22 or day 50 (3 weeks after the last vaccination), for all 4 influenza strains, the upper bound of the 2-sided 95% CI on the difference between the seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody remained within the non-inferiority margin of 10% (6.9% for A/H1N1, 9.2% for A/H3N2, 4.5% for B1 and 3.2% for B2 influenza strains) (Table 15).

Table 15: Non-inferiority of QIVc relative to TIVc in children and adolescents 4 to less than 18 years of age – Per-protocol analysis set

		QIVc	**TIV1c/TIV2c[b]**	**Vaccine Group Ratio**	**Vaccine Group Difference**
A/H1N1		N = 1014	N = 510		
	GMT (95% CI)	1090 (1027-1157)	1125 (1034-1224)	1.03 (0.93-**1.14**)	-
	Seroconversion Rate (95% CI)	72% (69-75)	75% (70-78)	-	2% (-2.5-**6.9**)
A/H3N2		N = 1013	N = 510		
	GMT (95% CI)	738 (703-774)	776 (725-831)	1.05 (0.97-**1.14**)	-
	Seroconversion Rate (95% CI)	47% (44-50)	51% (46-55)	-	4% (-1.4-**9.2**)
B1		N = 1013	N = 510		
	GMT (95% CI)	155 (146-165)	154 (141-168)	0.99 (0.89-**1.1**)	-
	Seroconversion Rate (95% CI)	66% (63-69)	66% (62-70)	-	0% (-5.5-**4.5**)
B2		N = 1009	N = 501		
	GMT (95% CI)	185 (171-200)	185 (166-207)	1 (0.87-**1.14**)	-
	Seroconversion Rate (95% CI)	73% (70-76)	71% (67-75)	-	-2% (-6.5-**3.2**)

[a] For H1N1, H3N2 and B1 influenza strains ratio of seroconversion and vaccine group difference was calculated as TIV1c/QIVc, whereas for B2 influenza strain ratio of seroconversion and vaccine group difference was calculated as

TIV2c/QIVc. Analysis is performed on day 22 for previously vaccinated subjects and day 50 for not previously vaccinated subjects. **Bold**: Non-inferiority is met if the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMTTIV1c or TIV2c /GMTQIVc) for HI antibody does not exceed the non-inferiority margin of 1.5. Non-inferiority is met if the upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody does not exceed the margin of 10%.

1) Secondary Immunogenicity Objectives: superiority of antibody responses to the first influenza B strain (B1) in QIVc as compared to TIV2c (containing the alternative influenza B (B2) strain) and the second B influenza strain (B2) in QIVc as compared to TIV1c (containing the B1 influenza strain) as assessed by GMT ratios and seroconversion rates in subjects ≥4 to <18 years of age.

At day 22 or day 50 (3 weeks after the last vaccination), superiority as assessed by the ratio of GMTs and differences in seroconversion rates was established for the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain).

Geometric Mean Titres

At day 22 or day 50 (3 weeks after the vaccination), the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV2c /GMT QIVc) for HI antibody remained within the superiority margin of 1 (2 sided 95% CI: 0.35-0.42).

Table 16: GMT and Ratios (95% CI), Against B1 Strain, 3 weeks after the last vaccination, HI Assay – Full Analysis set

	QIVc	TIV2c	Vaccine Group ratios
	N=1112	N=557	
Day 22 or day 50[a]	154 (145-163)	59 (54-64)	0.38 (0.35-**0.42**)

Superiority is met if the upper bound of the 2-sided 95% CI for the ratio of GMTs (GMT TIV2c /GMT QIVc) for HI antibody does not exceed the superiority margin of 1. [a] Analysis is performed on day 22 for previously vaccinated subjects and day 50 for not previously vaccinated subjects.

Similar results were seen for the B2 strain (GMTs 176 QIVc vs 45 TIV1c, ratio 0.25 (0.22-**0.29**)).

Seroconversion

At day 22 or day 50 (3 weeks after the vaccination), the upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV1c or TIV2c – % seroconversion QIVc) for HI antibody did not exceed the margin of 0 points (2 sided 95% CI:-38.8%- -29.3%).

Table 17: Number (%) of subjects with seroconversion (95% CI) against B1 strain, 3 weeks after the last vaccination, HI Assay – Full analysis set

	QIVc	TIV2c	Vaccine Group Difference
	N=1112	N=557	
Day 22 or day 50[a]	743 (67%) (64%-70%)	182 (33%) (29%-37%)	-34% (-38.8%, -**29.3**%)

Superiority is met if the upper bound of the 2-sided 95% CI for the difference between seroconversion rates (% seroconversion TIV2c - %seroconversion QIVc) for HI antibody does not exceed the margin of 0 points. [a] Analysis is performed on day 22 for previously vaccinated subjects and day 50 for not previously vaccinated subjects.

Similar results were seen for the B2 strain (SCR 73% QIVc vs 26% TIV1c, ratio -47% (-51.1%, -**42.1**%).

2) Secondary Immunogenicity Objective: Assessment of vaccine immunogenicity based on CBER and CHMP immunogenicity criteria in subjects 4 to <18 years of age

At day 22 or day 50 (3 weeks after the last vaccination), both CBER immunogenicity criteria for seroconversion and HI titre ≥1:40 were met for A/H1N1, A/H3N2, B1 and B2 influenza strains by the QIVc and the TIV1c/TIV2c vaccines. CBER immunogenicity criteria are as follows: The lower bound of the 2-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%. The lower bound of the 2-sided 95% CI for the percentage of subjects achieving an HI antibody titre ≥1:40 should meet or exceed 70%.

At day 22 or day 50 (3 weeks after the last vaccination), all 3 CHMP immunogenicity criteria for seroconversion, HI titre ≥1:40 and GMR were met for A/H1N1, A/H3N2, B1 and B2 influenza strains by the QIVc and the TIV1c/TIV2c vaccines. CHMP immunogenicity criteria were: i) the percentage of subjects with seroconversion or significant increase in HI antibody is >40%; ii) the percentage of subjects achieving an HI titre ≥1:40 is >70%; iii) the GMR is >2.5.

3) Exploratory Immunogenicity Objectives: these were not performed by the applicant in light of the fact that the primary research questions were addressed satisfactorily.

Additional post-hoc analyses

The applicant performed analyses in study population subsets according to age, sex/gender, race/ethnicity, baseline immune status, previous vaccination status, and history of medical conditions that might increase the risk for complications from influenza. The Clinical trials were not powered to evaluate non-inferiority of QIVc to TIVc in these subgroups, and thus within each group descriptive comparisons were made between GMTs, seroconversion rates, and subjects achieving a HI titre ≥40.

Overall, the analyses did not show any striking difference between the TIVc and QIVc within the different subgroups analysed. In particular, children from 4 to <9 years and from 9 to < 18 years seronegative at baseline had comparable immune response after vaccination with QIVc against all strains, as indicated by both high percentages of subjects with post-vaccination titre ≥1:40 and high seroconversion rates at Day 22/Day50. Similar rates were obtained after vaccination with TIVc for both age sub-groups. For subjects with titres ≥1:10 at baseline, the HI titres and seroconversion rates were also comparable between both age sub-groups.

2.5.3. Ancillary analyses

The following ancillary analyses were performed with TIVc. The applicant has no plans to conduct further studies with QIVc to investigate persistence of antibodies, revaccination and concomitant administration with other vaccines, considering that these data are already available with TIVc and that the addition of the second B strain to the vaccine does not diminish the potency of QIVc. This was found acceptable.

Persistence of antibody response

Persistence of antibodies was evaluated in 2 studies performed with TIVc, which were already assessed during the MAA for Optaflu: study V58P9 and study V58P4.

V58P9 is a phase III, randomized, controlled, observer-blind, multi-centre study to evaluate safety and immunogenicity of a single dose of three lots of a trivalent cell culture-derived (N=1029) or of a trivalent egg-derived vaccine (N=171) in adults 18 to <61 years of age. Persistence of antibodies against the 3 viral strains contained in the TIVc and TIVe vaccines was evaluated in study V58P9 up to and also after the

6-month follow-up period, which is the more important period, since the northern hemisphere influenza season lasts from November until April.

In study V58P9, GMTs and percentages of subjects with HI titre ≥ 40 at baseline against all 3 viral strains were mostly similar in the TIVc and control groups. Similarly, GMTs increased by approximately 8- to 9-fold against the B strain and 14- to 18-fold against the 2 A strains 3 weeks after vaccination, at which time 88% to 96% of subjects across both TIVc and control groups were seroprotected across strains. For both the TIVc and control groups there was a slight decline in HI titre ≥ 1:40 rates against the A strains from 3 weeks to 6 months (decrease range: 14% to 17%). Nonetheless, the lower limit of the 95% CIs for HI titre ≥ 40 against both A strains remained above the CBER minimum requirement of 70% (range: 75% to 80%). There was a greater decline in the percentages of seroprotected subjects against the B strain (decrease range 25% to 28%) and for both TIVc and control groups and the lower limit of the 95% CI fell below 70% (range: 57% to 65%). This could not be accounted for by a difference in baseline HI titre ≥ 1:40 rates, as they were similar for the A/H3N2 and B strains. After 6 months, the GMTs in both TIVc and TIVe groups had fallen to about half the value that was measured at 3 weeks against all 3 viral strains, thus remaining higher for the A strains (range: 6.2- and 7.51-fold over baseline across vaccine groups) than for the B strain (3.87- and 3.53-fold over baseline for TIVc and control groups, respectively), which is important since influenza season lasts until April in the Northern Hemisphere and protection may extend over the entire season.

In **Study V58P4,** a total of 1067 adults 18 to < 61 years of age and 1168 adults ≥ 61 years of age were enrolled and vaccinated. In the extension study V58P4E1, subjects received vaccines in the subsequent influenza season to that of study V58P4. Following WHO recommendations, 2 of the 3 viral strains included in the vaccine composition of the V58P4E1 study remained the same, whereas the A/H3N2 strain changed from A/Wyoming/3/2003 IVR-X-147 (used in V58P4) to A/New York/55/2004-X-157 [H3N2] (used in V58P4E1). As after 1 year sera were tested against the strains included in the vaccine composition of that year, antibody titre persistence could only be assessed against the 2 unchanged vaccine strains (A/New Caledonia/20/99 IVR-116 [H1N1] and B/Jiangsu/10/2003). The evaluation of antibody persistence was based on the serological assessment of HI titre ≥ 1:40 and GMTs. Subjects from each vaccine group in study V58P4 were randomly assigned (1:1) to receive either TIVc or control (TIVe, Agrippal) vaccine in the extension study. Subsets of 239 adults 18 to < 61 years of age and 245 adults ≥ 61 years of age were enrolled for the immunogenicity analyses.

Adults 18 to < 61 Years of Age – V58P4E1

In study V58P4, GMTs and percentages of subjects with HI titre ≥ 40 at baseline against all 3 viral strains were similar in the TIVc and control groups. GMTs similarly increased by approximately 6- to 13- fold across strains at 3 weeks after vaccination for the TIVc and control vaccines in study V58P4, at which time 90% to 99% of subjects across TIVc and control groups were seroprotected. Although for the 2 conserved viral strains (A/H1N1 and B) GMTs had fallen after 1 year to about one fourth their previous value, rates of HI titre ≥ 40 remained high (TIVc 57%, control 51% A/H1N1 strain; TIVc 54%, control 52% B strain). However, as expected, the GMTs and HI titre ≥ 40 rates of the new A/H3N2 strain (changed from the previous year's vaccines used in study V58P4) were low at the start of the extension study V58P4E1 (GMTs: 18 and 19 for the TIVc and control groups; HI titre ≥ 40 rates: 29% for both the TIVc and control groups).

Adults ≥ 61 Years of Age – V58P4E1

In adults ≥ 61 years of age, in study V58P4 GMTs and HI titres ≥ 40 at baseline against all 3 viral strains were similar in the TIVc and control groups. GMTs similarly increased by approximately 5- to 12-fold across strains at 3 weeks after vaccination with the TIVc and control vaccines in V58P4, at which time

85% to 98% of subjects across vaccine group were seroprotected. Although for the 2 conserved viral strains (A/H1N1 and B) the GMTs had fallen after 1 year to about one third to one fourth of their previous value, HI titre ≥ 40 rates remained high (TIVc 48%, control 36%, A/H1N1 strain; TIVc 61%, control 52%, B strain). However, as expected, GMTs and HI titre ≥ 40 rates for the new A/H3N2 strain (changed from the previous year's vaccines used in V58P4) were low at the start of the extension study V58P4E1 (GMTs: 20 for TIVc and 22 for control group; HI titre ≥ 40 rates: 32% for TIVc and 33% for control group).

Effect of Revaccination in V58P4E1

Generally, the type of vaccine received in study V58P4 had no impact on the immunogenicity results of the adult vaccination groups for the A/New Caledonia/20/99 (H1N1) strain or the B/ Shanghai/361/2002 (B) strain in this study. For the A/California/7/2004 (H3N2) strain, there was a trend towards lower post-vaccination GMRs in the TIVe group:

- Adults 18 to < 61 Years of Age: GMRs 5.03 TIVe vs. 9.32 TIVc;
- Adults ≥ 61 Years of Age: GMRs: 7.01 TIVe vs. 12 TIVc.

Effect of Concomitant Vaccination with Pneumococcal Vaccine in Study V58P4E2

The primary immunogenicity objective of study V58P4E2 was to assess the non-inferiority of the influenza vaccines when administered alone (FLU group = pooled TIVc and TIVe groups) or concomitantly with pneumococcal vaccine (FLU+PV group) for the 3 tested strains, in the randomized elderly population (≥ 65 years of age). Non-inferiority required that the lower limit of the 2-sided 95% confidence interval (CI) of the ratio of the post-vaccination (i.e., extension study Day 22) GMTs (FLU+PV/FLU vaccine alone) be greater than 0.5.

At baseline, the lowest GMTs were detected against the B viral strain and the highest against the A/H3N2 viral strain (A/H1N1: 22 and 26, A/H3N2: 67 and 83, B: 15 and 18, in the FLU and FLU+PV vaccine groups respectively). At extension study Day 22, 3 weeks post-vaccination, GMTs increased against each of the 3 viral strains, ranging from 36 and 52 for the B strain, up to 184 and 228 for the A/H3N2 viral strain.

The lower limit of the 95% CI of the ratio of the post-vaccination GMTs between the 2 vaccine groups (FLU+PV and FLU alone) was greater than 0.5 against one (A/H3N2) of the 3 viral strains (A/H1N1: 0.45, A/H3N2: 0.55, B: 0.46). The primary objective of non-inferiority of FLU+PV to FLU was not met in the other 2 strains probably because the sample size was too low due to a high dropout rate and many exclusions. The main reason for exclusion from the immunogenicity PP set was that subjects randomized to the FLU group had also received PV (22 subjects in the TIVc group vs 11 subjects in the TIVe group). Out of 147 subjects enrolled in FLU and 122 subjects enrolled in FLU+PV vaccine groups, only 77 subjects from FLU and 74 subjects from FLU+PV constituted the immunogenicity PP set. Because the point estimates for post-vaccination GMTs between the 2 vaccine groups were above 0.5 against all 3 viral strains (range, 0.66 to 0.81), it was assumed that the objective was not reached due to the small sample size and the corresponding wide CI.

This was confirmed by analyses on the modified per protocol population (MPP). The increased sample size of the MPP, where non-inferiority was demonstrable for 2 out of the 3 strains, suggests that the primary objective results would have been met if the PP size had been larger.

2.5.4. Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well

as the benefit risk assessment (see later sections).

Table 18: Summary of efficacy data for study V130_01

Title: A Phase III, Stratified, Randomized, Double-Blind, Multicenter, NonInferiority Study to Evaluate the Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine and Cell-based Trivalent Subunit Influenza Virus Vaccines in **Adults ≥18 Years of Age.**				
Study identifier	V130_01			
Design	Stratified, Randomized, Double-Blind, Multicenter			
	Duration of main phase:	day 1 (vaccination) through day 22		
	Duration of Run-in phase:	not applicable		
	Duration of Extension phase:	not applicable		
Hypothesis	Non-inferiority			
Treatments groups	QIVc	A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Massachusetts/2/2012 [B1], B/Brisbane/60/2008 [B2]		
	TIV1c	A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Massachusetts/02/2012 [B1]		
	TIV2c	A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Brisbane/60/2008 [B2]		
Objectives and endpoints	Primary endpoint n°1	To demonstrate non-inferiority of antibody responses of QIVc to comparator, as assessed by the ratio of GMT at 3 weeks after vaccination (day 22) for each of the 4 vaccine strains.		
	Primary endpoint n°2	To demonstrate non-inferiority of antibody responses of QIVc to comparator TIVc 3 weeks after vaccination (day 22), as assessed by differences in seroconversion rates for each of the 4 vaccine strains separately after vaccination.		
	Key Secondary endpoint	To evaluate the antibody responses to all 4 influenza vaccine strains after vaccination in 2 age cohorts, ≥18 years to <65 years of age and ≥65 years of age, according to the CBER criteria as defined for the different age-cohorts.		
	Secondary endpoint	To evaluate the antibody responses to all 4 influenza vaccine strains after vaccination in the 2 age cohorts: ≥18 to <60 years and ≥61 years according to the CHMP criteria		
	Secondary endpoint	To demonstrate superiority of antibody responses to the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain) as assessed by GMT ratios and seroconversion rates in adults ≥18 years of age.		
	Secondary endpoint	To demonstrate superiority of antibody responses to the second B strain (B2) in QIVc as compared to TIV1c (containing the B1 strain) as assessed by GMT ratios and seroconversion rates in adults ≥18 years of age.		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	PPS – Per protocol set			
Descriptive statistics and estimate	Treatment group	QIVc	TIV1c	TIV2c
	Number of subject	1250	635	638

variability	GMT (Day 22)	A/H1N1 = 302.8 A/H3N2 = 372.3 B1 = 133.2 B2 = 177.2	A/H1N1 = 298.9 A/H3N2 = 378.4 B1 = 115.6 B2 = 164.0
	95%CI	A/H1N1 = 281.8-325.5 A/H3N2 = 349.2-396.9 B1 = 125.3-141.7 B2 = 167.6-187.5	A/H1N1 = 270.3-330.5 A/H3N2 = 345.1-414.8 B1 = 106.4-125.6 B2 = 151.4-177.7
	Seroconversion (Day 22)	A/H1N1 = 615 (49.2%) A/H3N2 = 479 (38.3%) B1 = 457 (36.6%) B2 = 497 (39.8%)	A/H1N1 = 309 (48.7%) A/H3N2 = 226 (35.6%) B1 = 221 (34.8%) B2 = 226 (35.4%)
	95%CI	A/H1N1 =46.4%-52.0% A/H3N2 =35.6%-41.1% B1 = 33.9%-39.3% B2 = 37.0%-42.5%	A/H1N1 = 44.7%-48.7% A/H3N2 = 31.9%-39.5% B1 = 31.1%-38.7% B2 = 31.7%-39.2%
Effect estimate per comparison	**Primary endpoint n°1**	Comparison groups	Vaccine group ratio ($GMT_{TIV1c/TIV2c}/GMT_{QIVc}$)
		GMT	A/H1N1 = 1.0 A/H3N2 = 1.0 B1 = 0.9 B2 = 0.9
		95%CI	A/H1N1 = 0.9-**1.1** A/H3N2 = 0.9–**1.1** B1 = 0.8-**1.0** B2 = 0.9-**1.0**
		Non-inferiority met if the upper limit of the two-sided 95% CI for the ratio of GMTs is < 1.5	
	Primary endpoint n°2	Comparison groups	Vaccine group difference (Seroconversion rate TIV1c/TIV2c – seroconversion rate QIVc.)
		Seroconversion rate	A/H1N1 = -0.5% A/H3N2 = -2.7% B1 = -1.8% B2 = -4.4%
		95%CI	A/H1N1 = -5.3%-**4.2**% A/H3N2 = -7.2%-**1.9**% B1 = -6.2%-**2.8**% B2 = -8.9%-**0.2**%
		Non-inferiority met if the upper limit on the difference seroconversion rates for each strain is <10%	
Effect estimate per comparison	**Secondary endpoint**	Superiority of antibody responses to the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain)	
	Treatment group	QIVc	TIV2c
	Number of subject	1311	657
	GMT (Day 22)	117.1	76.3
	95%CI	167.8-187.1	70.4-82.7
	Ratio of GMT	0.5	
	95%CI	0.5-**0.5**	
		Superiority met if the upper limit of the two-sided 95% CI for the ratio of GMTs is < 1	
	Seroconversion rates (Day 22)	39.7%	18.0%
	95%CI	37.0%-42.4%	15.1%-21.1%
	Difference of Seroconversion rates	-21.7%	
	95%CI	-25.5%, **-17.7%**	
		Superiority met if the upper limit on the difference seroconversion rates for each strain is <0%	

	Secondary endpoint	superiority of antibody responses to the second B strain (B2) in QIVc as compared to TIV1c (containing the B1 strain)	
	Treatment group	QIVc	TIV1c
	Number of subject	1311	664
	GMT (Day 22)	135.4	91.7
	95%CI	127.6-143.7	85.7-98.2
	Ratio of GMT	0.6	
	95%CI	0.6-**0.7**	
		Superiority met if the upper limit of the two-sided 95% CI for the ratio of GMTs is < 1	
	Seroconversion rates (Day 22)	36.6%	17.2%
	95%CI	34.0%-39.3%	14.4%-20.3%
	Difference of Seroconversion rates	-19.4%	
	95%CI	-23.2%, **-15.5%**	
		Superiority met if the upper limit on the difference seroconversion rates for each strain is <0%	

The pre-specified non-inferiority objectives for all the 4 strains are reached since the upper limit of the two-sided 95% CI:

- for the ratio of GMTs is < 1.5 for each strain,
- on the difference seroconversion rates for each strain is < 10%

The superiority was shown for the 2 B strains since the upper limits of the two-sided 95% CI:

- for the ratios of GMTs were < 1
- on the difference seroconversion rates is < 0

Table 19: Summary of efficacy data for study V130_03

Title: A Phase III, Stratified, Randomized, Double-Blind, Multicenter, Non-Inferiority Study to Evaluate Safety and Immunogenicity of Cell-Based Quadrivalent Subunit Influenza Virus Vaccine and Cell-Based Trivalent Subunit Influenza Virus Vaccines in Subjects **Aged ≥4 Years to <18 Years**		
Study identifier	V130_03	
Design	Stratified, Randomized, Double-Blind, Multicenter	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	day 1 (vaccination) through day 22/50 not applicable not applicable
Hypothesis	Non-inferiority	
Treatments groups	QIVc	A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Massachusetts/2/2012 [B1], B/Brisbane/60/2008 [B2]
	TIV1c	A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Massachusetts/02/2012 [B1]

	TIV2c		A/Brisbane/10/2010 [H1N1], A/Texas/50/2012 NYMC X-223A [H3N2], B/Brisbane/60/2008 [B2]
Endpoints and definitions	Primary endpoint n°1	To demonstrate non-inferiority of antibody responses of QIVc to comparator TIVc in subjects ≥4 to <18 years of age, as assessed by the ratio of GMT for each of the 4 vaccine strains separately after vaccination.	
	Primary endpoint n°2	To demonstrate non-inferiority of antibody responses of QIVc to comparator TIVc after vaccination in subjects ≥4 to <18 of age years, as assessed by differences in seroconversion rates for each of the 4 vaccine strains separately after vaccination.	
	Secondary endpoint	To evaluate the antibody responses to all 4 influenza vaccine strains after vaccination according to the CBER criteria as defined for the different age-cohorts.	
	Secondary endpoint	To evaluate the antibody responses to all 4 influenza vaccine strains after vaccination according to the CHMP criteria	
	Secondary endpoint	To demonstrate superiority of antibody responses to the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain) as assessed by GMT ratios and seroconversion rates.	
	Secondary endpoint	To demonstrate superiority of antibody responses to the second B strain (B2) in QIVc as compared to TIV1c (containing the B1 strain) as assessed by GMT ratios and seroconversion rates.	

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	PPS – Per protocol set			
Descriptive statistics and estimate variability	Treatment group	QIVc	TIV1c	TIV2c
	Number of subject	1014	510	502
	GMT (Day 22 or Day 50)	A/H1N1 = 1090 A/H3N2 = 738 B1 = 155 B2 = 185	A/H1N1 = 1125 A/H3N2 = 776 B1 = 154 B2 = 185	
	95%CI	A/H1N1 = 1027-1157 A/H3N2 = 703-774 B1 = 146-165 B2 = 171-200	A/H1N1 = 1034-1224 A/H3N2 = 725-831 B1 = 141-168 B2 = 166-207	
	Seroconversion (Day 22 or Day 50)	A/H1N1 = 732 (72%) A/H3N2 = 473 (47%) B1 = 672 (66%) B2 = 735 (73%)	A/H1N1 = 380 (75%) A/H3N2 = 258 (51%) B1 = 336 (66%) B2 =357 (71%)	
	95%CI	A/H1N1 = 69%-75% A/H3N2 = 44%-50% B1 = 63%-69% B2 = 70%-76%	A/H1N1 = 70%-78% A/H3N2 = 46%-55% B1 = 62%-70% B2 =67%-75%	
Effect estimate per comparison	**Primary endpoint n°1**	Comparison groups	Vaccine group ratio ($GMT_{TIV1c/TIV2c}/GMT_{QIVc}$)	
		GMT (Day 22 or Day 50)	A/H1N1 = 1.03 A/H3N2 = 1.05 B1 = 0.99 B2 = 1	
		95%CI	A/H1N1 = 0.93-**1.14** A/H3N2 = 0.97–**1.14** B1 = 0.89-**1.1** B2 = 0.87-**1.14**	
		Non-inferiority met if the upper limit of the two-sided 95% CI for the ratio of GMTs is < 1.5		

	Primary endpoint n°2	Comparison groups	Vaccine group difference (Seroconversion rate TIV1c/TIV2c – seroconversion rate QIVc.)
		Seroconversion rate (Day 22 or Day 50)	A/H1N1 = 2% A/H3N2 = 4% B1 = 0% B2 = -2%
		95%CI	A/H1N1 = -2.5%-6.9% A/H3N2 = -1.4%-9.2% B1 = -5.5%-4.5% B2 = -2%-3.2%
		Non-inferiority met if the upper limit on the difference seroconversion rates for each strain is <10%	
Effect estimate per comparison	**Secondary endpoint**	Superiority of antibody responses to the first B strain (B1) in QIVc as compared to TIV2c (containing the B2 strain)	
	Treatment group	QIVc	TIV2c
	Number of subject	1112	557
	GMT (Day 22)	154	59
	95%CI	145-163	54-64
	Ratio of GMT	0.38	
	95%CI	0.35-**0.42**	
		Superiority met if the upper limit of the two-sided 95% CI for the ratio of GMTs is < 1	
	Seroconversion rates (Day 22)	67%	33%
	95%CI	64%-70%	29%-37%
	Difference of Seroconversion rates	-34%	
	95%CI	-38.8%, **-29.3%**	
		Superiority met if the upper limit on the difference seroconversion rates for each strain is <0%	
	Secondary endpoint	Superiority of antibody responses to the second B strain (B2) in QIVc as compared to TIV1c (containing the B1 strain)	
	Treatment group	QIVc	TIV1c
	Number of subject	1108	563
	GMT (Day 22)	176	45
	95%CI	164-189	41-19
	Ratio of GMT	0.25	
	95%CI	0.22-**0.29**	
		Superiority met if the upper limit of the two-sided 95% CI for the ratio of GMTs is < 1	
	Seroconversion rates (Day 22)	73%	26%
	95%CI	70%-76%	23%-30%
	Difference of Seroconversion rates	-47%	
	95%CI	-51.1%, **-42.1**%	

		Superiority met if the upper limit on the difference seroconversion rates for each strain is <0%

The pre-specified non-inferiority objectives for all the 4 strains are reached since the upper limit of the two-sided 95% CI:

- for the ratio of GMTs is < 1.5 for each strain,
- on the difference seroconversion rates for each strain is < 10%.

The superiority was shown for the 2 B strains since the upper limits of the two-sided 95% CI:

- for the ratios of GMTs were <1,
- on the difference seroconversion rates is <0.

2.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analyses or meta-analyses were performed across trials. Immunogenicity data were not pooled for several reasons: the studies were conducted in various influenza seasons, various TIVc formulations with different strains were administered, and the HI assay is high variable.

In this context, it is agreed that integration of immunogenicity data does not provide useful information.

Immunogenicity data across trials are summarised in the following tables.

Adult and elderly subjects

Results in adults <65YOA (Table 20) obtained with the QIVc vaccine were robust and generally consistent with results obtained with the TIVc vaccines in this age group. For TIVc similar results were seen against licensed egg-based comparator.

Results obtained in older adults >65YOA with the QIVc vaccine were consistent with results obtained with the TIVc vaccines in this age group. Subjects > 75 years of age were only included in QIVc study V130_01 and TIVc study V58P4. Age stratification for those > 75 years of age was not part of study design, but these subjects were analysed separately for the purposes of this submission. In the > 75 years of age subgroups, results obtained with the QIVc vaccine indicated that immune responses were less robust than in the overall elderly group ≥65 years of age. Results obtained with TIVc were generally similar in the > 75 years of age subgroup and the overall elderly group ≥61 years of age consistent with results obtained with the TIVe vaccines in this age group.

Table 20: Immunogenicity Results (GMTs, GMRs, Seroconversion Rates) Across Studies in Adults, by Strain

	Adults 18 to < 50 years		**Adults 18 to < 61 years**		**Adults 18 to < 61 years**		**Adults 18 to < 50 years**		**Adults 18 to < 65 years**	
	V58P13*		**V58P4***		**V58P9***		**V58_23****		**V130_01*****	
	TIVc	**TIVeA**	**TIVc**	**TIVeA**	**TIVc**	**TIVeA**	**TIVc**	**TIVeF**	**TIV1c**	**QIVc**
	n = 228	**n = 695**	**n = 650**	**n = 644**	**n = 1017**	**n = 168**	**n = 1143**	**n = 379**	**n = 309**	**n = 629**
Strain: A/H1N1										
Prevaccination GMT	34 (27-42)	35 (31-40)	16 (15-18)	18 (16-19)	16 (14-17)	17 (14-21)	85 (78-94)	73 (60-88)	49.8 (41.1-60.4)	53.3 (46.8-60.8)
Postvaccination GMT	566 (483-663)	499 (455-546)	185 (167-205)	186 (167-206)	275 (253-299)	281 (229-346)	688 (644-735)	1226 (1083-1388)	472.2 (429.4-519.2)	432.2 (374.7-498.5)
GMR	17	14	11	11	18	16	8.08	17	8.7	8.9
Seroconversion rate	78%	75%	69%	67%	81%	77%	60%	69%	60.2%	63.3%
Strain: A/H3N2										
Prevaccination GMT	48 (39-58)	41 (37-46)	46 (42-51)	43 (39-48)	13 (12-14)	14 (12-16)	108 (99- 117)	126 (108-148)	102.2 (85.1-122.6)	99.9 (88.3-113)
Postvaccination GMT	332 (289-383)	357 (330-387)	278 (258-300)	307 (285-332)	186 (172-200)	234 (195-281)	457 (429-486)	820 (732-919)	410.5 (361.5-466)	414.1 (379.4-452)
GMR	6.94	8.68	5.99	7.08	14	17	4.24	6.49	4	4.1
Seroconversion rate	59%	68%	63%	64%	83%	88%	49%	63%	46.6%	49.1%
	Adults 18 to < 50 years		**Adults 18 to < 60 years**		**Adults 18 to < 61 years**		**Adults 18 to < 49 years**		**Adults 18 to < 65 years**	
	V58P13*		**V58P4***		**V58P9***		**V58_23****		**V130_01*****	
	TIVc	**TIVeA**	**TIVc**	**TIVeA**	**TIVc**	**TIVeA**	**TIVc**	**TIVeF**	**TIV1c**	**QIV**
	n = 228	**n = 695**	**n = 650**	**n = 644**	**n = 1017**	**n = 168**	**n = 1144**	**n = 379**	**n = 309**	**n = 629**
Strain: B/Yam										
Prevaccination GMT	14 (12-16)	13 (12-14)	10 (9.56-11)	11 (10-12)	13 (12-13)	13 (11-15)	57 (54-62)	34 (30-37)	42.4 (37.2-48.4)	42.9 (39.1-47.1)
Postvaccination GMT	72 (63-84)	120 (111-131)	139 (127-152)	131 (119-143)	124 (115-132)	109 (92-128)	174 (165-184)	111 (101-122)	167.7 (149.5-188.1)	186.6 (171-203.5)
GMR	5.2	9.41	13	12	9.76	8.29	3.03	3.3	4	4.3
Seroconversion rate	51%	68%	85%	81%	85%	81%	39%	45%	50.5%	52%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; HI = hemagglutination inhibition; N/E = not evaluated; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent influenza vaccine; TIVc = cell-based trivalent influenza vaccine; TIV1c = TIVc formulation containing all 3 WHO recommended strains for trivalent influenza virus vaccine composition (including B/Massachusetts); TIVeA = egg-based trivalent influenza vaccine (Agrippal); TIVeF = egg-based trivalent influenza vaccine (Fluvirin).
* Egg assay.

** Full analysis set: TIVc contained A/Brisbane/10/2010 [H1N1], TIVeF contained A/Christchurch/16/2010 [H1N1], samples from TIVc vaccinated subjects tested by HI assay using cell-based vaccine strains. Samples from TIVeF vaccinated subjects tested by HI assay using egg-based influenza strains.
*** Cell assay.
Figures in parentheses are 95% confidence intervals.

Paediatric subjects 4 to <18 YOA

Results obtained with the QIVc vaccine were robust and consistent with results obtained with the TIVc vaccines overall in this age group, as seen in the 2 following tables split per subgroup.

Table 21: Immunogenicity Results (GMTs, GMRs, Seroconversion Rates) Across Studies in Paediatric Subjects 4 to < 9 Years of Age, Cell-based Assay

	V58P12		**V130_03**	
	TIVc	**TIVe**	**TIV1c**	**QIVc**
Strain: A/H1N1	**n = 441**	**n = 430**	**n = 238**	**n = 467**
Prevaccination GMT	21 (18-25)	18 (16-22)	102 (81-128)	90 (77-106)
Postvaccination GMT (Day 50)	609 (540-686)	685 (608-773)	1109 (990-1242)	1042 (962-1130)
GMR	29	34	11	11
Seroconversion rate	96%	97%	77%	75%
	V58P12		**V130_03**	
	TIVc	**TIVe**	**TIV1c**	**QIVc**
Strain: A/H3N2	**n = 441**	**n = 430**	**n = 238**	**n = 467**
Prevaccination GMT	83 (42-52)	102 (37-45)	200 (163-246)	183 (158-212)
Postvaccination GMT (Day 50)	976 (855-1114)	1743 (1527-1989)	782 (709-863)	758 (707-813)
GMR	12	17	4	4.09
Seroconversion rate	80%	87%	48%	52%
	V58P12		**V130_03**	
	TIVc	**TIVe**	**TIV1c**	**QIVc**
Strain: B/Yam	**n = 441**	**n = 430**	**n = 238**	**n = 467**
Prevaccination GMT	8.54 (5.87-6.52)	9.32 (5.99-6.65)	15 (13-18)	18 (16-20)
Postvaccination GMT (Day 50)	60 (51-71)	71 (60-84)	116 (102-132)	117 (106-128)
GMR	7.02	7.61	7.21	6.75
Seroconversion rate	62%	62%	69%	71%
	V130_03			
	TIV2c		**QIVc**	
Strain: B/Vic	**n = 236**		**n = 464**	
Prevaccination GMT	21 (18-25)		19 (17-21)	
Postvaccination GMT (Day 50)	166 (141-195)		161 (143-181)	
GMR	8.21		8.34	
Seroconversion rate	75%		74%	

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; QIVc = cell-based quadrivalent influenza vaccine; TIVc = cell-based trivalent influenza vaccine; TIVe = egg-based trivalent influenza vaccine; TIV1c = TIVc formulation containing all 3 WHO recommended strains for trivalent influenza virus vaccine composition (including B/Massachusetts); TIV2c = TIVc formulation containing both WHO recommended A strains for trivalent influenza virus vaccine composition and the influenza B/Brisbane strain from the alternate Victoria lineage; TIVeA = egg-based trivalent influenza vaccine (Agrippal).
Numbers in parentheses are 95% confidence intervals.

Table 22: Immunogenicity Results Across Studies in Paediatric Subjects 9 to < 18 Years of Age

	V58P12		**V130_03**	
	TIVc*	**TIVeA***	**TIV1c***	**QIVc****
Strain: A/H1N1	**n = 142**	**n = 144**	**n = 272**	**n = 547**
Prevaccination GMT	70 (53-92)	90 (69-119)	98 (81-119)	102 (89-116)
Postvaccination GMT Day22/29	1076 (886-1307)	1296 (1069-1571)	1138 (1007-1286)	1139 (1045-1242)
GMR	15	14	12	11
Seroconversion rate	74%	74%	72%	70%
Strain: A/H3N2	**n = 142**	**n = 144**	**n = 272**	**n = 547**
Prevaccination GMT	125 (98-158)	144 (114-182)	194 (165-227)	230 (205-257)
Postvaccination GMT Day22/29	676 (585-783)	1651 (1429-1908)	762 (694-836)	719 (673-767)
GMR	5.45	11	3.79	3.19
Seroconversion rate	52%	78%	53%	42%
Strain: B/Yam	**n = 142**	**n = 144**	**n = 272**	**n = 547**
Prevaccination GMT	22 (18-27)	25 (21-30)	35 (30-40)	37 (33-41)
Postvaccination GMT (Day 29)	136 (113-163)	186 (155-222)	200 (178-224)	200 (185-218)
GMR	6.15	7.37	5.69	5.43
Seroconversion rate	63%	69%	63%	63%

	V130_03	
	TIV2c*	**QIVc****
Strain: B/Vic	**n = 316**	**n = 547**
Prevaccination GMT	26 (22-30)	27 (24-30)
Postvaccination GMT Day 29	203 (175-234)	212 (192-235)
GMR	7.82	7.91
Seroconversion rate	68%	72%

Abbreviations: GMR = geometric mean ratio; GMT = geometric mean titer; QIVc = cell-based quadrivalent influenza vaccine; TIVc = cell-based trivalent influenza vaccine; TIV1c = TIVc formulation containing all 3 WHO recommended strains for trivalent influenza virus vaccine composition (including B/Massachusetts); TIV2c = TIVc formulation containing both WHO recommended A strains for trivalent influenza virus vaccine composition and the influenza B/Brisbane strain from the alternate Victoria lineage; TIVeA = egg-based trivalent influenza vaccine (Agrippal).
* Egg assay.
** Cell assay.
Numbers in parentheses are 95% confidence intervals.

2.5.6. Clinical studies in special populations

No dedicated clinical trials with QIVc were performed in special populations. The elderly were included in study V130_01. The table below, details the numbers of adult subjects in the development program that received TIVc or QIVc per age category. There have been no non-controlled studies. The majority of subjects (73%) who received either QIVc or TIVc were within the 65 to 74 years old age group. Analyses in the various subgroups indicated similar immune response in TIVc as compare to QIVc.

Table 23: Counts of Subjects in Age Categories 65-74, 75-84, and 85+ in Four Studies

		Age 65-74 (number of older subjects / total number)	**Age 75-84 (number of older subjects / total number)**	**Age 85+ (number of older subjects / total number)**	**Total 65+ TIVc/QIVc**
Controlled studies	Study	TIVc or QIVc	TIVc or QIVc	TIVc or QIVc	
	V58P1	21 (84%)	4 (16%)	0 (0%)	25
	V58P2	26 (68%)	12 (32%)	0/ (0%)	38
	V58P4	385 (76%)	118 (23%)	6 (1%)	509
	V130_01	465 (70%)	173 (26%)	22 (3%)	1340
	Total:	**897 (73%)**	**307 (25%)**	**28 (2%)**	1232

Study V58P4, for both TIVc and control vaccines, evaluated a subset of subjects (N = 448) with cardiovascular and pulmonary conditions as well as diabetes mellitus. The study measured immune responses against the CHMP criteria and all 3 criteria were passed. Overall, it was observed that both vaccines induced good immune responses even in at risk subjects with underlying medical conditions

2.5.7. Supportive studies

The QIVc clinical development program is supported by studies of the TIVc, which have already been assessed during the MAA and post-authorisation procedures of Optaflu:

- one TIVc efficacy study (V58P13) in adults 18 to < 50 years of age;
- antibody persistence and immunogenicity after repeated vaccination, and effect of concomitant vaccination (V58P9,V58P4, V58P4E1, V58P4E2): refer to section 2.5.3;
- Three paediatric TIVc studies to support the indication in 4-18 years old subjects as claimed by the applicant for QIVc considering that Optaflu is only indicated to adults >18 years of age:
    1. Study V58P12, a combined Phase ll/lll, observer-blind, randomized, multi-centre study to evaluate safety and immunogenicity of TIVc in healthy children and adolescents aged 3 to 17 years. This study was assessed in procedure EMEA/H/C/758/FUM 14 and EMEA/H/C/758/FUM34 for Optaflu.
    2. 2 phase III studies, V58P15 and V58_31, to evaluate only safety. These studies were assessed in Optaflu procedure EMEA/H/C/000758/P46-0052 and EMEA/H/C/000758/P46-0053 respectively.

The main ones based on relevance for this application are summarised in this section. The phase 1 and 2 studies (V58P1, V58P2, and V58P5) with a small number of subjects exposed (< 400 subjects), will not be presented to describe immunogenicity. Study V58_23 evaluated lot-to-lot consistency of 3 consecutive lots of TIVc manufactured in Holly Springs and of a comparator TIVeF group in subjects 18 to < 49 years of age using GMT and seroconversion rates at 3 weeks after vaccination (Day 22) for each of the 3 vaccine strains. Each vaccine group was further evaluated according to the immunogenicity criteria defined by CBER.

Immunogenicity data were not pooled because integration of immunogenicity data would not provide useful information since the studies were conducted in various influenza seasons, with administration of various TIVc formulations with differing strains, and because of the high variability of the HI assay.

The large scale immunogenicity studies in adults ≥ 18 years of age (V58P13, V58P4, V58P9, and V58_23) and in pediatric subjects 4 to < 18 years (V58P12), have demonstrated robust immune responses to TIVc. Specifically, noninferiority to licensed egg-based comparators for all strains in persons ≥ 18 years of age and to the A/H1N1 and B strains for persons 4 to < 18 years of age was shown.

Study V58P13

The study was assessed in procedure EMEA/H/C/758/FUM39. A type II variation was submitted in February 2014 to reflect data of the V58P13 clinical efficacy study in section 5.1 of the SmPC (EMEA/H/C/758/II/0063). A positive opinion was adopted on 25 April 2014 by the CHMP.

Study V58P13 is a phase III, three armed randomized (trivalent cell culture-derived influenza vaccine, trivalent egg-derived influenza vaccine (Agrippal), placebo) observer-blind, placebo-controlled, multi-centre study performed over a period of approximately 9 months at multiple study sites in the US, Poland and Finland. Both cell culture- and egg-derived influenza vaccines contained 15 µg for each of the three vaccine strains (A/H1N1, A/H3N2 and B) recommended for the 2007-2008 influenza season, for a total IM volume dose of 0.5 ml.

A total of 11,404 subjects were enrolled to receive TIVc (N = 3828), TIVeA (N = 3676) or placebo (N = 3900) in a 1:1:1 ratio. Among the overall study population enrolled, the mean age was 33 years, 55% were female, 84% were Caucasian, 7% were Black, 7% were Hispanic, and 2% were of other ethnic origin.

Study Objectives

Two primary objectives were defined:

- To demonstrate protection of a cell culture-derived influenza (CCI) virus vaccine compared with placebo against illness caused by virus-confirmed community-acquired influenza wild type strains antigenically similar to those contained in the vaccines.
- To demonstrate protection of an egg-derived influenza virus vaccine (IVV) compared with placebo against illness caused by virus-confirmed community-acquired influenza wild type strains antigenically similar to those contained in the vaccines.

Secondary efficacy objectives included i) to evaluate protection against lab-confirmed ILI regardless of antigenic matching and of protection against "dissimilar" strains; ii) to evaluate the effect on reduction of number of days in bed, the number of in- and outpatient medical visits due to ILI or influenza like symptoms; and iii) to evaluate the effect on the number of days of usual activity lost.

Secondary immunogenicity endpoints were to evaluate seroprotection (HI titre ≥1:40) and seroconversion in a subset (HI titre <1:10, post-vaccination titre ≥1: 40; in subjects with baseline HI titre ≥1:10, a ≥4-fold increase in post-vaccination HI antibody titre).

Safety objectives were to evaluate the safety and tolerability of cell culture derived and egg derived influenza vaccine.

Outcomes/endpoints

Efficacy

The primary endpoint was virus-confirmed influenza like illness (ILI). Clinical efficacy was defined as the prevention of culture-confirmed symptomatic influenza illness caused by viruses antigenically matched to those in the vaccine compared to placebo. The secondary endpoint was vaccine efficacy against culture-confirmed influenza caused by vaccine-like and non-vaccine-like strains (i.e., circulating strains).

The CDC-case definition of ILI was applied, which is a fever of ≥37.8°C and cough or sore throat. Influenza cases were identified by active and passive surveillance of influenza-like illness (ILI). Definitive diagnosis of influenza "illness" required laboratory confirmation of influenza virus. During the surveillance period (1 November 2007 to 30 April 2008), symptoms of influenza that met the study criteria for obtaining nasal and throat specimens for evaluation of the presence of influenza virus, as well other symptoms of influenza (body aches, chills, headache and runny/stuffy nose) were collected. After an episode of ILI, nose and throat swab samples were collected for analysis. For individual subjects, collection of specimens for influenza virus testing should not have started any earlier than 3 weeks following their vaccination. Tissue culture and PCR testing for influenza virus was performed at a central laboratory. Antigenic characterization was performed on positive samples in a different central laboratory. Vaccine efficacies against vaccine-matched influenza viral strains, against all influenza viral strains, and against individual influenza viral subtypes were calculated.

Results

A total of 11,299 subjects in the enrolled population, who had received a study vaccination, were included in the efficacy MITT population. The MITT population for the efficacy analyses included 3790, 3648, 3861 subjects in the CCI vaccine, IVV and Placebo groups, respectively. The efficacy PP population included 11,257 subjects and included 3776, 3638, and 3843 subjects form the CCI vaccine, IVV and placebo group, respectively.

VE against vaccine-like strains and against all strains

The rates of culture-confirmed influenza caused by vaccine-like strains in the per protocol efficacy population were 0.0019 (7/3776) in the CCI group and 0.0114 (44/3843) in the placebo group (VE = 83.8%; 97.5% CI lower limit: 61%). Thus the primary efficacy endpoint, overall vaccine efficacy relative to placebo against vaccine-like strains, was achieved for both TIVc and TIVeA (Table 24). For the A/H1N1 strain the associated VE and lower limit (LL) of the simultaneous one-side 97.5% CI were 88.2% and 67.4%, respectively. For strain B, the VE was 100% as no influenza cases were reported in the CCI vaccine group, while one case was reported in the placebo group, therefore cases are too few to adequately assess efficacy. Additionally, for the A/H3N2 strain, the VE of the CCI vaccine vs. placebo was not evaluable since no influenza case was observed in the placebo group (Table 25).

The secondary endpoint of vaccine efficacy against culture-confirmed influenza caused by vaccine-like and non-vaccine-like strains (i.e., all circulating strains) was also achieved for both vaccines (Table 24).

Table 24: Vaccine efficacy against culture-confirmed influenza, study V58P13

	Number of subjects per protocol	Number of subjects with influenza	Attack Rate (%)	Vaccine Efficacy*	
				%	Lower Limit of 1-Sided 97.5% CI
Antigenically Matched Strains					
TIVc	3776	7	0.19	83.8	61.0
TIVeA	3638	9	0.25	78.4	52.1
Placebo	3843	44	1.14	--	--
All Culture-Confirmed Influenza (Matched and Unmatched Strains)					
TIVc	3776	42	1.11	69.5	55.0
TIVeA	3638	49	1.35	63.0	46.7
Placebo	3843	140	3.64	--	--

Abbreviations: CI = confidence interval; TIVc = cell-based trivalent influenza vaccine; TIVeA = egg-based trivalent influenza vaccine (Agrippal).
* Simultaneous 1-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the 2 relative risks.
Vaccine Efficacy = (1 - Relative Risk) x 100%.

Table 25: Comparative efficacy of TIVc and TIVeA vs. placebo against culture-confirmed influenza by influenza viral subtype, study V58P13

	TIVc (N = 3776)		TIVeA (N = 3638)		Placebo (N = 3843)		TIVc Vaccine Efficacy*		TIVeA Vaccine Efficacy*	
	Attack Rate (%)	Number of Subjects with Influenza	Attack Rate (%)	Number of Subjects with Influenza	Attack Rate (%)	Number of Subjects with Influenza	%	Lower Limit of One-Sided 97.5% CI	%	Lower Limit of One-Sided 97.5% CI
Antigenically Matched Strains										
A/H3N2*	0.05	2	0.03	1	0	0	N/E	N/E	N/E	N/E
A/H1N1	0.13	5	0.22	8	1.12	43	88.2	67.4	80.3	54.7
B**	0	0	0	0	0.03	1	100.0	-410.0	100.0	-429.4
All Culture-Confirmed Influenza (Matched and Unmatched strains)										
A/H3N2	0.16	6	0.33	12	0.65	25	75.6	35.1	49.3	-9.0
A/H1N1	0.16	6	0.27	10	1.48	57	89.3	73.0	81.5	60.9
B	0.79	30	0.74	27	1.59	61	49.9	18.2	53.2	22.2

Abbreviations: CI = confidence interval; N/E = not evaluable; TIVc = cell-based trivalent influenza vaccine; TIVeA = egg-based trivalent influenza vaccine (Agrippal).
* Simultaneous 1-sided 97.5% confidence intervals for the vaccine efficacy of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the 2 relative risks. Vaccine Efficacy = (1 - Relative Risk) x 100%.
** There were too few cases of influenza due to vaccine-matched influenza A/H3N2 or B to adequately assess vaccine efficacy.

VE against Non-vaccine-like strains

The rates of culture-confirmed influenza caused by non-vaccine-like strains in the per protocol efficacy population were 0.0079 (30/3776) in the CCI group and 0.0193 (74/3843) in the placebo group (VE = 58.7%). The lower limit of the simultaneous one-sided 97.5% CI for the overall VE of the CCI vaccine vs. placebo was 33.5% (p=0.078). Similar results were observed for the CCI vaccine group in the MITT population.

Table 26: Vaccine Efficacy Against Culture-Confirmed Influenza Caused by Non-Vaccine-like Strains – Per Protocol Population - V58P13

	Proportion of Subjects with Influenza (# Subjects)			VE (%)[1]		Simultaneous 97.5% CI of VE[1]		P-value[2]	
	CCI (N=3776)	IVV (N=3638)	Placebo (N=3843)	CCI vs Placebo	IVV vs Placebo	CCI vs Placebo	IVV vs Placebo	CCI vs Placebo	IVV vs Placebo
Overall	0.0079 (25/3776)	0.0080 (29/3638)	0.0193 (74/3843)	58.7	58.6	33.5	32.9	0.0784	0.0846
A/H3N2	0 (0/3776)	0.0005 (2/3638)	0.0021 (8/3843)	100.0	73.6	36.3	-30.0	0.0296	0.2651
A/H1N1	0.0003 (1/3776)	0 (0/3638)	0.0021 (8/3843)	87.3	100.0	4.6	33.9	0.1037	0.0327
B	0.0077 (29/3776)	0.0074 (27/3638)	0.0154 (59/3843)	50.0	51.7	17.5	19.4	0.3756	0.3185

[1] Simultaneous one-sided 97.5% confidence intervals for the vaccine efficacy (VE) of each influenza vaccine relative to placebo based on the Sidak-corrected score confidence intervals for the two relative risks. VE = Vaccine Efficacy = (1 - Relative Risk) x 100%

[2] Adjusted p-values are from the score statistic with Sidak correction testing the null hypothesis that the vaccine efficacy of each influenza vaccine relative to placebo <= 40% against the alternative hypothesis that the VE > 40% (or equivalently, the null hypothesis that the relative risk (RR) >= 0.60 vs. the alternative hypothesis that RR <0.60). If the adjusted p-value is < 0.025, then the comparison is statistically significant.

Study V58P12

Study V58P12 was a combined phase 2/3, observer-blind, randomized, multicentre study to evaluate safety, tolerability, and immunogenicity of TIVc and an egg-derived vaccine Fluvirin (TIVf) in children 3 to <18 years of age. A reanalysis of data for 4 to <18 year old subjects was conducted after a request from CBER because the comparator vaccine in the study was not licensed in the US in subjects <4 years of age. In the 3 to < 9 years of age group, only influenza vaccine-naïve subjects were considered, and they received 2 vaccine administrations.

In the original study, a total of 3604 subjects were enrolled and randomized in 3 cohorts: 974 in Cohort 1 and 2 (9-17 years of age) and 2630 in cohort 3 (3-8 years of age). Subjects in Cohort 2 (669 subjects aged 9 to 17 years, randomized at a 3:1 ratio to receive TIVc or egg-derived vaccine) were evaluated for safety only, while subjects in Cohort 3 were stratified into two age groups (6 to 8 years and 3 to 5 years), for a total of 1304 subjects in the 6 to 8 years age and 1326 subjects in the 3 to 5 years age strata, respectively.

With the exclusion of < 4 years of age subjects (N=464) from cohort 3, a total of 3140 subjects of 4-17 years of age were enrolled: 974 in cohorts 1 and 2 (9-17 years of age) and 2166 in cohort 3 (4-8 years of age). For immunogenicity purposes, subjects in each age group were randomized at a 1:1 ratio (certain sites were only included in the safety subset and these were randomised to a 2:1 ratio).

Outcomes/endpoints

Co-Primary Immunogenicity Objectives

The primary objective in study V58P12 was non-inferior immunogenicity of TIVc to TIVeF for all 3 strains after 2 doses administered 4 weeks apart to children 4 to < 9 years of age. The antibody responses assessed were HI GMT and percentages of subjects with seroconversion at day 50 post-vaccination, i.e. after two injections administered four weeks apart to children aged 4 to 8 years:

- The non-inferiority of TIVc compared to TIVf, measured by HI GMTs at day 50 would be established if, for all 3 strains, the lower limit of the 95% confidence interval (CI) for post-vaccination day 50 ratio of GMTs (TIVc/TIVf) is greater than 0.667.
- The non-inferiority of TIVc compared to TIVf, measured by seroconversion and significant increase at day 50 would be established if, for all 3 strains, the lower limit of the 95% CI for

differences of percentages of seroconversion and significant increase (TIVc minus TIVf) is greater than -10%.

The analysis population for the primary immunogenicity objective (4-8 years) was the PP population.

Secondary Immunogenicity Objectives

To evaluate immunogenicity, measured by seroprotection and by the percentage of subjects achieving seroconversion or significant increase according to a) the CHMP criteria as per guideline CPMP/BWP/214/96 and b) CBER criteria as per relevant FDA Guidelines, following:

- one injection of TIVc or egg-derived vaccine administered to children and adolescents aged 9 to 17 years (Cohort 1);
- two injections of TIVc or egg-derived vaccine administered four weeks apart to children aged 3 to 8 years (Cohort 3, immunogenicity subset).

Results

There were 2166 subjects enrolled in Cohort 3; 1330 in TIVc and 836 in TIVf groups. 9% of subjects in each group were withdrawn from the study before the study end. The primary reasons for withdrawal were lost to follow-up and withdrawal of consent. Two subjects were withdrawn from the study due to AEs assessed by the investigator to be unrelated to the study vaccine.

Overall, 12% of subjects in TIVc group and 18% of subjects in TIVf group had major protocol deviations. The most common protocol deviations were: subjects received second vaccination outside the window period, subjects did not receive second vaccination and subjects did not provide all serum samples and all immunogenicity results.

Immunogenicity results

Study V58P12 showed a robust immune response in the vaccine-naïve 4 to < 9 years of age group and in the 9 to < 18 years age group:

Table 27: Immunogenicity Results at 3 Weeks After Last Vaccination in Pediatric Subjects, Study V58P12, Cell-based HI Assay – PPS

		V58P12 Subjects 4 to < 9 Years Not Previously vaccinated (Cohort 3)		**V58P12 Subjects 9 to < 18 Years (Cohort 1)**	
	Day 22/Day 50	**TIVc N = 441**	**TIVeF N = 430**	**TIVc N = 142**	**TIVeF N = 144**
A/H1N1	GMT (95% CI)	609 (540-686)	685 (608-773)	1076 (886-1307)	1296 (1069-1571)
	GMR	29	34	15	14
	SCR[a]	96%	97%	74%	74%
A/H3N2	GMT (95% CI)	976 (855-1114)	1743 (1527-1989)	676 (585-783)	1651 1429-1908
	GMR	12	17	5.45	11
	SCR[a]	80%	87%	52%	78%
B1	GMT (95% CI)	60 (51-71)	71 (60-84)	136 (113-163)	186 (155-222)
	GMR	7.02	7.61	6.15	7.37
	SCR[a]	62%	62%	63%	69%

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titre; HI = haemagglutination inhibition; PPS = per protocol set; SCR = seroconversion rate; TIVc = cell-based trivalent influenza vaccine; TIVeF = egg-based trivalent influenza vaccine (Fluvirin).
a Defined as a negative pre-vaccination titre (< 1:10) and post-vaccination HI ≥ 1:40 or at least a 4-fold increase from a positive baseline titre (≥ 1:10).
***** cell-based assay.

The results for the co-primary endpoints are reflected in the following 2 tables.

Table 28 shows that the pre-specified non-inferiority objectives for the A/H3N2 strain are not reached in cohort 3 (4-9YOA) since the lower limit of the two-sided 95% CI for the ratio of GMTs (TIVc/TIVf) is < 0.67 (0.47) and on the difference seroconversion rates (TIVc-TIVf) is <-10%. Same results were observed in the ITT population.

It is of note that, in the initial population (3-8 years of age) for which this study was powered to demonstrate non inferiority of TIVc to TIVf, for the H3N2 strain non-inferiority was only observed for seroconversion and not for GMTs.

Table 28: Immunogenicity Response in Cohort 3 (4-8 years of age) at Day 50, HI Assay- PP Population

		TIVc	TIVf	Ratio of GMTs TIVc/TIVf (95% CI)	Vaccine group Difference TIVc-TIVf (95%CI)
		HI cell-derived antigen assay			
A/H1N1	GMTs	609 (540, 686)	685 (608, 773)	0.89 (**0.76**, 1.04)	
	Seroconversion or significant increase	424 (96%) (94%, 98%)	415 (97%) (94%, 98%)		0% (**-3**%, 2%)
A/H3N2	GMTs	976 (855, 1114)	1743 (1527, 1989)	0.56 (0.47, 0.67)	
	Seroconversion or significant increase	353 (80%) (76%, 84%))	375 (87%) (84%, 90%)		-7% (-12%, -2%)
B	GMTs	60 (51, 71)	71 (60, 84)	0.85 (**0.68**, 1.06)	
	Seroconversion or significant increase	273 (62%) (57%, 66%)	265(62%) (57%, 66%)		0% (**-6%,** 7%)

In Table 29, high baseline antibody titres were observed against the A/H3N2 strain in both age groups. Against A/H1N1 and B strains, in both vaccine groups, the pre-vaccination GMT and the percentage of subjects with titre >1:40 are low in the sub-group 4-5 years of age.

The analysis by age sub-groups (4-5 years of age and 6-8 years of age) shows that, in the 6-8 years group, against the A/H3N2 strain, GMT, GMR and SCR are significantly lower in the TIVc group compared to the TIVf group (95%CI do not overlap), while the GMT at baseline were similar between the groups.

Overall against the A strains, in both groups, TIVc induced an acceptable antibody response with high percentage of subjects with titre >1:40 (SPR >97%). However, against the B strain, in the sub-group 4-5 years of age, SCR and percentage of subjects with titre >1:40 is quite low (50% and 51% respectively), significantly lower than the one observed in the 6-8 years group. Reverse cumulative distribution curves

for the HA response against the B strain in the age subgroups 4 to 5 years and 6 to 8 years were thus presented. In the subgroup of children 4 to 5 years who received TIVc, 51.1 % (LL 95% CI 43.7%) of the children have titres ≥1:40; in children 6 to 8 years this is 74.1% (LL 95% CI 68.2%).

Table 29: Immunogenicity Results of Subjects 4-5 years of age and 6-8 years of age

	4-5 years		**6-8 years**	
	TIVc N=190	TIV1f N=181	TIVc N=251	TIV1f N=249
A/H1N1				
Prevaccination GMT (95%CI)	12 (9.57; 16)	11 (8.35; 14)	30 (24; 37)	26 (21; 32)
Day 50 GMT (95%CI)	446 (355; 561)	505 (403; 631)	749 (649; 866)	833 (719; 964)
GMR (D50/prevaccination) (95%CI)	36 (26; 46)	47 (38; 59)	25 (21; 30)	32 (27; 38)
Day 50 SCR (95%CI)	96% (92; 98)	95% (91; 98)	96% (93; 98)	98% (95; 99)
Prevaccination SPR (95%CI)	24% (18; 30)	18% (13; 25)	51% (44; 57)	49% (43; 56)
Day 50 SPR (95%CI)	97% (94; 99)	97% (93; 99)	100% (98; 100)	100% (98; 100)
A/H3N2				
Prevaccination GMT (95%CI)	58 (43; 78)	86 (64; 117)	**102 (84; 124)**	**109 (90; 134)**
Day 50 GMT (95%CI)	796 (599; 1057)	1337 (1012; 1767)	**1045 (914; 1195)**	**2089 (1822; 2394)**
GMR (D50/prevaccination) (95%CI)	14 (11; 17)	15 (12; 20)	**10 (8.49; 12)**	**19 (16; 23)**
Day 50 SCR (95%CI)	85% (79; 90)	85% (78; 89)	76% (71: 82)	89% (85; 93)
Prevaccination SPR (95%CI)	71% (64; 77)	74% (67; 80)	**78% (73; 83)**	**87% (82; 91)**
Day 50 SPR (95%CI)	98% (95; 99)	93% (89; 97)	100% (98; 100)	100% (98; 100)
B1				
Prevaccination GMT (95%CI)	7.38 (6.45; 8.43)	7.86 (6.9; 8.96)	10 (9.1; 12)	11 (9.57; 12)
Day 50 GMT (95%CI)	38 (29; 52)	46 (35; 62)	92 (74; 114)	100 (81; 124)
GMR (D50/prevaccination) (95%CI)	5.21 (4.16; 6.54)	5.89 (4.72; 7.35)	8.89 (7.46; 11)	9.19 (7.68; 11)
Day 50 SCR (95%CI)	**50% (43; 57)**	48% (40; 55)	71% (65; 76)	72% (66; 77)
Prevaccination SPR (95%CI)	8% (5; 13)	10% (6; 16)	14% (10; 19)	17% (13; 23)
Day 50 SPR (95%CI)	**51% (44; 58)**	49% (42; 57)	74% (68:79)	78% (72; 83)

The antibody responses seen in the 9-18 years of age group were consistent with those seen in the clinical study in adults in which efficacy of the vaccine was demonstrated (V58P13). Both studies were conducted in the 2007/2008 Northern Hemisphere Influenza Season.

Table 30: Post-vaccination Geometric Mean Titre Comparisons for TIVc Vaccinated Subjects in the 2007/2008 Northern Hemisphere Influenza Season, Egg-based HI Assay (V58P12 and V58P13)

	V58P12 (Subjects 9 to < 18 Years)		V58P13 (Subjects 18 to 49 Years)	
	TIVc	**TIVeF**	**TIVc**	**TIVeA**
A/H1N1	879 (728-1062)	1107 (918-1334)	566 (483-663)	499 (455-546)
A/H3N2	706 (607-821)	1857 (1598-2157)	332 (289-383)	357 (330-387)
B	58 (48-71)	105 (86-129)	72 (63-84)	120 (111-131)

Abbreviations: HI = hemagglutination inhibition; TIVc = cell-based trivalent influenza vaccine; TIVeA = egg-based trivalent influenza vaccine (Agrippal); TIVeF = egg-based trivalent influenza vaccine (Fluvirin).

Immunogenicity results with the egg-based Hi assay

The use of cell-derived reagents resulted in higher GMTs compared with egg-derived reagents for both vaccines (statistical non-inferiority criteria was not met for the H3N2 and B strain in the 4-8 year-olds, data not shown). The seed viruses used to manufacture TIVc and QIVc used in all of the trials included in this dossier were passaged in eggs prior to manufacture using MDCK cells. Both the TIVe and TIVc vaccines used in study V58P12 were manufactured using egg-derived virus seed. Given the antigenic similarity of the seed viruses, the different outcomes for the egg and cell reagents may more likely be attributable to the variability of the HI assay.

Immunogenicity results by immune status at baseline

The applicant has presented a comparison of the immunogenicity data of TIVc versus TIVe in subjects who were seronegative at baseline for both groups of age. Although according to the V58P12 study protocol, all subjects 4 to < 9 years of age who received two doses of influenza vaccine in one season were excluded from enrolment, a substantial percentage of subjects in the PPS had detectable baseline HI titres. As expected, the percentages of enrolled children seronegative at baseline were lower in age group 4-9 YOA (~60% for H1N1, ~15% for H3N2 and ~83% for B strains) as compared to subjects 9-18 YOA (~20%, 6% and 62% for the 3 strains respectively). For the 4-9 YOA, the immune response to TIVc was in general comparable to TIVeF. However, this was not the case for subjects 9-18 YOA, for whom the HI titres against H1 virus were higher for the TIVc group vs. TIVeF, but the HI titres against the H3 and B strains were lower.

Table 31: V58P12 immunogenicity Results at 3 Weeks After Last Vaccination in Subjects 4 to < 9 and 9 to < 18 Years of Age, Seronegative at baseline (HI <1:10), egg-derived HI Assay – PPS

		4 to < 9 years (cohort 3)		9 to < 18 years (cohort 1)	
		TIVc	TIVe	TIVc	TIVe
A/H1N1	Day 1 Prevaccination (95% CI)	N = 260 5 (5-5)	N = 260 5 (5-5)	N = 29 5 (5-5)	N = 11 5 (5-5)
	Day 1 % HI Titre ≥ 1:40 (95% CI)	0% (0%-1%)	0% (0%-1%)	0% (0%-12%)	0% (0%-28%)
	Day 29/ Day 50 GMT (95% CI)	203 (173-238)	273 (234-319)	459 (269-784)	198 (82-477)
	GMR (95% CI)	41 (35-48)	55 (47-64)	92 (54-157)	40 (16-95)
	Day 29/ Day 50 % HI Titre ≥ 1:40 (95% CI)	95% (92%-98%	97% (94%-99%)	97% (82%-100%)	91% (59%-100%)
	Seroconversion Rate (95% CI)	95% (92%-98%)	97% (94%-99%)	97% (82%-100%)	91% (59%-100%)
A/H3N2	Day 1 Prevaccination (95% CI)	N = 70 5 (5-5)	N = 54 5 (5-5)	N = 9 5 (5-5)	N=5 5 (5-5)
	Day 1 % HI Titre ≥ 1:40 (95% CI)	0% (0%-5%)	0% (0%-7%)	0% (0%-34%)	0% (0%-52%)
	Day 29/ Day 50[a] GMT (95% CI)	150 (94-238)	145 (86-246)	266 (131-542)	1553 (637-3786)
	GMR (95% CI)	30 (19-48)	29 (13-38)	53 (26-108)	311 (127-757)
	Day 29/ Day 50 % HI Titre ≥ 1:40 (95% CI)	84% (74%-92%)	78% (64%-88%)	100% (66%-100%)	100% (48%-100%)
	Seroconversion Rate (95% CI)	84% (74%-92%)	78% (64%-88%)	100% (66%-100%)	100% (48%-100%)
B1	Day 1 Prevaccination (95% CI)	N = 370 5 (5-5)	N = 346 5 (5-5)	N = 88 5 (5-5)	N = 88 5 (5-5)
	Day 1 % HI Titre ≥ 1:40 (95% CI)	0% (0%-1%)	0% (0%-1%)	0% (0%-4%)	0% (0%-4%)
	Day 29/ Day 50[a] GMT (95% CI)	19 (16-22)	35 (29-41)	50 (37-67)	93 (69-126)
	GMR (95% CI)	3.73 (3.16-4.4)	6.92 (5.85-8.19)	9.94 (7.38-13)	19 (14-25)
	Day 29/ Day 50 % HI Titre ≥ 1:40 (95% CI)	34% (29%-39%)	50% (45%-55%)	68% (57%-78%)	77% (67%-86%)
	Seroconversion Rate (95% CI)	34% (29%-39%)	50% (45%-55%)	68% (57%-78%)	77% (67%-86%)

Abbreviations: HI = haemagglutination inhibition; PPS = per protocol set; GMT = geometric mean titre; GMR = geometric mean titre ratio; CI = confidence interval. Seroconversion rate = percentage of subjects with either a pre-vaccination HI titre < 1:10 and post-vaccination HI titre ≥ 1:40 or with a pre-vaccination HI titre ≥ 1:10 and a minimum 4-fold increase in post-vaccination HI antibody titre

2.5.8. Discussion on clinical efficacy

Design and conduct of clinical studies

In general, the design of the two phase III studies conducted to evaluate the safety and efficacy (immunogenicity) of the QIVc in children 4 to < 18 years of age (V130_03 clinical study) and in adults 18 to > 75 years of age (V130_01 clinical study) is considered adequate.

Both studies were double blind (subjects, investigators, laboratories and sponsor were blinded to vaccine assignments). Subjects in each trial were randomized 2:1:1 to receive QIVc, TIV1c, or TIV2c (each of the TIVC containing one of the two B strains included in QIV). Adults (trial V130_01) received a single dose of vaccine whereas children (trial V130_03) received one or two doses of vaccine depending on their previous vaccination status.

Both trials (particularly trial V130_01) included subjects with underlying diseases (such as respiratory, cardiovascular and metabolic diseases) which are representative of the risk groups for which the influenza vaccine is routinely recommended. Pregnant women were excluded from the trials. The applicant has indicated that analysis of vaccine effectiveness stratified by risk group, including pregnant women, is planned as part of the annual brand-specific influenza vaccine effectiveness studies conducted in the Development of Robust and Innovative Vaccine Effectiveness (DRIVE) project, and this is considered satisfactory.

The baseline characteristics of the enrolled subjects were well balanced between treatment groups and in both trials, there were a small percentage of subjects withdrawn from the study. The percentages and reason for discontinuation were similar in the three treatment groups, and there was no indication of selective discontinuation.

The definition and use of the PPS (Per Protocol Population Immunogenicity Set) population for immunogenicity comparisons is also considered adequate. The immunogenicity was measured using the haemagglutination inhibition (HI) assay, in agreement with current CHMP influenza vaccines guideline.

The objectives of the two trials with QIVc aimed at showing non-inferiority of the immune response of QIVc to comparator TIVc1 and TIVc2 vaccines. The design of the two pivotal clinical trials is considered appropriate.

Efficacy data and additional analyses

Immunogenicity data from the two pivotal clinical trials with QIVc

In both QIVc trials the two co-primary immunogenicity objectives (non-inferiority criteria as assessed by the ratio of GMTs and differences in seroconversion rates) were achieved for all 4 influenza strains, indicating non-inferiority of QIVc vaccine over the TIV1c for the 3 influenza strains (A/H1N1, A/H3N2 and B1) and TIV2c vaccine for B2 influenza strain. The non-inferiority margins for immunogenicity used in these studies were based on CBER guidance and adequately justified by the applicant (CBER guidance Clinical Data Needed to Support the Licensure of Seasonal Influenza Vaccines May 2007, refer to section 2.5.2 for specific endpoints).

GMTS 21 days post-vaccination in adults subjects in study V130_01 were A/H1N1 = 302.8, A/H3N2 = 372.3, B1 = 133.2 and B2 = 177.2 for QIVc. Seroconversions in the same study were A/H1N1 = 615 (49.2%), A/H3N2 = 479 (38.3%), B1 = 457 (36.6%) and B2 = 497 (39.8%). GMTs 21 days post-vaccination in children in study V130_03 were A/H1N1 = 1090, A/H3N2 = 738, B1 = 155 and B2 =

185. Seroconversions in the same study were A/H1N1 = 732 (72%), A/H3N2 = 473 (47%), B1 = 672 (66%) and B2 = 735 (73%).

Moreover, the secondary endpoint, which aimed at showing superiority of QIVc over TIV1c and TIV2c in antibody response to unmatched B strains as assessed by the ratio of GMTs and differences in seroconversion rates, was also achieved.

The other secondary endpoints based on meeting CBER and CHMP criteria are considered informative. Nonetheless, the applicant has shown here that most of the immunogenicity objectives based on fulfilment of the CBER and CHMP criteria were met in both trials. In a few cases the CBER or CHMP criteria were not met, but this does not question the immunogenicity of the QIVc vaccine.

The data from trial V130_03 show that children in both age subgroups of 4 to <9 years and 9 to < 18 years (seronegative at baseline) had comparable immune response after vaccination with QIVc against all strains. Similar results were observed for subjects seropositive (HI titres ≥1:10) at baseline. Thus, the vaccine induces an adequate immune response in both age groups independently on the serostatus at baseline.

The applicant has additionally performed immunogenicity analyses in subpopulations, taking into account the age, sex, race/ethnicity, baseline serostatus and previous vaccination status. The clinical trials were not powered to evaluate non-inferiority of QIVc to TIVc in these subgroups, and thus within each group the comparisons were made between GMTs, seroconversion rates and subjects achieving a HI titre ≥1:40. Overall, the analyses did not show any striking difference between the TIVc and QIVc within the different subgroups analysed.

Importantly, the applicant planned for some exploratory secondary objectives (measurement of neutralizing and anti-NA antibodies, and cell-mediated immunity) in both pivotal trials, which were not performed as the main objectives of the trials were satisfactorily addressed. However analysis of neutralizing antibodies will be performed in the ongoing clinical efficacy study V130_12 (subjects 2 to < 18 years of age), and in the two planned QIVc immunogenicity and efficacy studies V130_10 and V130_14 in 6 months to < 48 months of age, and this approach is considered acceptable. In relation to measuring the anti-NA antibodies and CMI response, the pivotal trials were performed before the current influenza vaccine guideline was implemented and this is the reason why these assays were not performed. This explanation is considered satisfactory.

Immunogenicity and efficacy data from the supportive TIVc studies

The efficacy data with TIVc are relevant to Flucelvax Tetra because both vaccines are manufactured using the same process and have overlapping compositions.

Study V58P13 was a phase III, three armed randomized (trivalent cell culture-derived influenza vaccine, trivalent egg-derived influenza vaccine (Agrippal), placebo), which investigated subjects between 18 and 45 YOA. The primary endpoint was virus-confirmed influenza like illness (ILI). Clinical efficacy was defined as the prevention of culture-confirmed symptomatic influenza illness caused by viruses antigenically matched to those in the vaccine compared to placebo. The secondary endpoint was vaccine efficacy against culture-confirmed influenza caused by vaccine-like and non-vaccine-like strains (i.e., circulating strains). The primary efficacy endpoint, i.e. overall vaccine efficacy relative to placebo against vaccine-like strains, was achieved for both TIVc (83.8%) and TIVeA (78.4%). The secondary endpoint of vaccine efficacy against culture-confirmed influenza caused by vaccine-like and non-vaccine-like strains (i.e., all circulating strains) was also achieved for both vaccines (TIVc 69.5%, TIVe 63%). Additionally, VE could be demonstrated for the A/H1N1 strain (VE 88.2%, and lower limit of the simultaneous one-side 97.5% CI was 67.4%). There were too few cases of influenza due to vaccine-matched influenza A/H3N2

or B to adequately assess vaccine efficacy. VE against all culture-confirmed ILI by strain was: 75.6% for H3N2, 89.3% for H1N1 and 49.9% for B strain.

Study V58P12 was a combined phase 2/3 study to evaluate safety, tolerability, and immunogenicity of TIVc and an egg-derived vaccine Fluvirin (TIVf) in children 3 to <18 years of age. A reanalysis of data for 4 to <18 year old subjects was conducted after a request from CBER because the comparator vaccine in the study was not licensed in the US in subjects <4 years of age. In the 3 to < 9 years of age group, only influenza vaccine-naïve subjects were considered, and they received 2 vaccine administrations.

The primary objective was non-inferior immunogenicity of TIVc to TIVeF for all 3 strains after 2 doses administered 4 weeks apart to children 4 to < 9 years of age. The antibody responses assessed were HI GMT and percentages of subjects with seroconversion at day 50 post-vaccination, i.e. after two injections administered four weeks apart to children aged 4 to 8 years. The analysis population for the primary immunogenicity objective (4-8 years) was the PP population.

The secondary immunogenicity objectives were to evaluate immunogenicity, measured by seroprotection and by the percentage of subjects achieving seroconversion or significant increase according to a) the CHMP criteria as per guideline CPMP/BWP/214/96 and b) CBER criteria as per relevant FDA Guidelines.

Study V58P12 showed a robust immune response in the vaccine-naïve 4 to < 9 years of age group and in the 9 to < 18 years age group. However whilst for subjects 9-18YOA HI titres in this age subset were generally higher than HI titres seen in adults in the efficacy study V58P13 (see Table 20), except for titres against the B strains, for subjects 4-8YOA the co-primary objective of TIVc non-inferiority vs. TIVeF was not met for the GMT ratios and SCRs against A/H3N2 when sera were tested with the cell-based antigen HI assay. These results raised uncertainties regarding the immunogenicity of TIVc in children and thus were further discussed with the CHMP Vaccine Working Party (see below).

Persistence of antibodies

Persistence of antibodies was evaluated in 2 supportive studies performed with TIVc: study V58P9 in subjects 18-61YOA and study V58P4E1 in subjects >18YOA. Both studies demonstrated that antibody titres induced by TIVc persisted for up to 1 year at significantly higher levels than prior to vaccination in both age groups. In adults 18 to < 61 years of age from study V58P9, HI titre ≥40 rates remained high 6 months after vaccination, especially against the 2 A influenza strains, for which the HI titre ≥40 criterion was still achieved by both TIVc and TIVe groups. For all 3 viral strains, GMTs remained approximately 3- to 7-fold above baseline, which is important, since the influenza season in the northern hemisphere lasts until April and protection may extend over the entire season. Both in adults 18 to < 61 and ≥61 years of age from study V58P4E1 for the 2 same vaccine strains used in study V58P4, HI titer ≥40 rates remained high and GMTs were still approximately 1.4- to 3-fold higher than 1 year previously, prior to vaccination in study V58P4.

Coadministration with other vaccines

No data was generated for QIVc in co-administration with other vaccines. Some data was however generated from a TIVc supportive study V58P4E2. The primary immunogenicity objective of study V58P4E2 was to assess the non-inferiority of the influenza vaccines TIVc and TIVe when administered alone or concomitantly with pneumococcal vaccine in an elderly population ≥ 65 years of age. The non-inferiority criterion was met only for the H3N2 strain but this is considered likely due to limited sample size (immunogenicity subset of 77 and 74 subjects in the 2 groups receiving influenza vaccines and pneumococcal vaccine respectively). Based on these data and on clinical experience with TIVc, it was concluded that QIVc can be given at the same time as other vaccines.

Additional expert consultation

The VWP discussed the available immunogenicity and efficacy data for the Flucelvax Tetra (QIVc) dossier for the initially proposed paediatric indication 4-<18 YOA. No efficacy data were generated with QIVc in any age group. Therefore, in order to support a conclusion on the likely efficacy of QIVc in the paediatric population aged 4-<18 years, the applicant proposed an immunobridging approach whereby the immune responses to QIVc were compared with those to TIVc (Optaflu, for which efficacy was previously demonstrated in adults aged 18-45 years) in study V130_03. The trial showed non-inferior immune responses to all four influenza strains between QIVc and two TIVc vaccines, each containing one of the two B strains in QIVc.

This approach to approval of unadjuvanted seasonal QIV vaccines via direct comparisons with licensed TIV vaccines is in line with the influenza vaccine guideline issued by the CHMP in 2016. In this specific case, the problem with this strategy is that Optaflu is not licensed in a paediatric population. Therefore to infer efficacy in children and assess use from 4 YOA as proposed by the applicant, the QIVc immune responses documented in study V130_03 have to be indirectly compared to those obtained with a vaccine licensed for paediatric use. Study V58P12 had previously compared immune responses between TIVc and a trivalent egg-based vaccine (TIVeF, Fluvirin), which is licensed for use in children 4YOA and older and some efficacy data in children are available for Fluvirin.

In principle, this indirect immunobridging approach is considered valid by the VWP. Furthermore, efficacy in older children and adolescents (9-18YOA) can be inferred by immunobridging to the prior demonstration of efficacy of TIVc in adults aged 18-45 years in V58P13. This efficacy study assessed the absolute efficacy of TIVc vs. placebo and the relative efficacy of TIVc vs. TIVeA (Agrippal). V58P12 and V58P13 were conducted in the same season (NH 2007/2008) with TIVc carrying the same strains. Serological testing in each trial was conducted in parallel, i.e. the applicant did not assay sera from the two trials in the same runs, which is recommended in the influenza guideline when immunobridging to efficacy data. Nevertheless, the VWP does not consider the parallel testing problematic in this case, because immune responses were evaluated using the same HI assay performed in the same company's laboratory. Therefore, the immunogenicity data from V58P12 and V58P13 are very important to support approval of QIVc from 4 to <18 YOA and careful consideration needs to be given to the results, especially since they differ between age subgroups.

When looking at the immunogenicity data generated in study V58P12, the VWP made the following considerations with regards to the age subgroups:

1) 4-8YOA: the co-primary objective of TIVc non-inferiority vs. TIVeF was not met for the GMT ratios and SCRs against A/H3N2 when sera were tested with the cell-based antigen HI assay. When egg-base antigens were used in the HI assay to test the same sera, immune responses to the A/H3N2 and B strains did not meet the non-inferiority criteria.

The VWP noted that the TIVc formulation at that time was produced from virus seed isolated in eggs and then grown in MDCK cells, whereas currently TIVc/QIVc are only produced using cell-based material. The potential impact of this difference on immune responses observed with cell vs. egg-based antigens is not understood and potentially adds to the complexity of the interpretation of the results. The VWP also noted that in the recent responses the applicant had analysed the HI titres from V58P12 based on antibody thresholds proposed to be linked to different levels of protection by various authors (Hobson, Black and others). However, due to the inherent variability of the HI assay, this analysis is of unknown relevance, since the HI thresholds proposed were determined from results obtained with different HI assays performed in different labs and with different antigens.

Looking at the data split by age subgroup (3-5 and 5-8YOA), the VWP noted that older children show overall higher immune responses such that the results in 5-8 year-olds approach those in adolescents in the same trial. Generally lower immune responses to B strains were observed across trials as well as lower baseline titres. This is often observed in influenza vaccine trials, but it should also be considered that in V58P13 efficacy was shown against B strains.

Overall, there was general agreement within the VWP that there are some remaining uncertainties regarding the adequacy of the immune responses to A/H3N2 and B strains documented in V58P12 in the age subset 4 to 8 years and the majority felt unconvinced that the available immunogenicity data could support approval in this age group. It was also pointed out that the ongoing efficacy trial (V130_12) may not be able to address these uncertainties because numbers of cases that will be accrued per strain and per age subgroup cannot be predicted and the study is not powered to demonstrate efficacy in age subgroups. However, if this trial does show overall efficacy across the age range 2-<18 years with no particular concerns for efficacy against specific strains, these data and the available immunogenicity data might be considered sufficient to support use from 4 YOA.

2) 9-18YOA: as discussed above, extrapolation of QIVc efficacy for this population is acceptably based on indirect immunobridging to adults aged 18-45 years in whom the efficacy of TIVc was demonstrated. HI titres in study V58P12 in this age subset were generally higher than HI titres seen in adults in the efficacy study V58P13, except for titres against the B strains, for which the immune responses could be viewed as comparable between age groups if the known HI variability is taken into account. Overall the VWP had no concerns with the data available for this population, which indicate overall that similar clinical protection as seen in young adults is highly likely. Therefore, it was considered that the available data support use of QIVc from 9 YOA.

2.5.9. Conclusions on clinical efficacy

In this clinical development, the applicant has followed the recommendations of three scientific advices posed to CHMP in recent years regarding the clinical development program. This program included two phase III studies conducted to evaluate the safety and efficacy (immunogenicity) of the QIVc in children 4 to < 18 years of age (V130_03 clinical study) and in adults 18 to > 75 years of age (V130_01 clinical study). In addition, this MAA includes supportive data obtained with a TIVc.

The two QIVc trials were appropriately designed and the two immunogenicity co-primary endpoints were met. Additionally the applicant has provided data from a clinical protection efficacy trial (V58P13) conducted with the trivalent formulation that serves as adequate support for the indication from ≥18 YOA. Based on the results from the adult study V130_01 and from the comparison with the efficacy and immunogenicity data generated from study V58P13, it can be concluded that QIVc is highly likely able to induce similar clinical protection in subjects 18YOA and above as seen with TIVc (Optaflu).

Concerning the paediatric population, during evaluation the applicant proposed an indication from 9 to 18 YOA, presenting data with QIVc (study V130_03) in comparison with TIVc and data with TIVc in comparison with TIVe (study V58P12). By indirect immunobridging, immune responses to QIVc, which were found non-inferior to the immune responses induced by TIVc, were compared with immune responses to TIVe (Fluvirin) both in adolescents and in adults, for whom efficacy was demonstrated. Fluvirin is authorised in individuals >4YOA in the EU and some efficacy data was also generated in children. Overall the data assessed indicate that QIVc is highly likely to induce similar clinical protection in children >9YOA, at least as good as the already licensed egg comparator vaccine.

The applicant commits to continue to monitor the performance of QIVc during the post-authorisation phase by means of an effectiveness study conducted in the context of the DRIVE project, as specified in

the RMP. In addition, the results of the ongoing efficacy study V130_12 should be submitted as soon as available.

2.6. Clinical safety

The clinical development program to support registration of QIVc in individuals 4 years of age and above builds on that of the TIVc development, which has demonstrated the safety, immunogenicity and efficacy of TIVc compared to licensed egg-based comparator.

Unpooled safety data from two clinical studies comparing QIVc with TIVc are available. Both studies (Study V130_01, Study V130_03) were phase 3 trials conducted in the US, in adults 18 years of age and above (including elderly adults), and in subjects 4 to < 18 years of age, respectively. Both studies used two trivalent, cell culture-derived vaccines as active comparators (each with a different influenza B strain, TIV1c and TIV2c).

In addition, safety data from 12 clinical studies performed with TIVc have been evaluated as supportive. These data were pooled into an adult data set (subjects ≥ 18 years of age) and a paediatric data set (subjects 4 to < 18 years of age). Integrated safety is only reported from studies with unique exposures and therefore does not include extension studies.

The TIVc clinical program demonstrated that the safety profile of TIVc is similar to that of egg-based comparator trivalent influenza vaccines.

The QIVc studies demonstrated that addition of a fourth strain does not alter the safety profile of QIVc, which remains similar to that of TIVc.

In addition to these clinical trial data, post marketing safety data for QIVc and TIVc is also available.

Patient exposure

A total of 2680 adults 18 years of age and above were enrolled in study V130_01, including 1340 elderly (≥65 years of age) subjects. The solicited safety set included 1319 subjects exposed to QIVc, 670 exposed to TIV1c, and 663 exposed to TIV2c, while the unsolicited safety set included 1324, 673, and 665 subjects in the QIVc, TIV1c, and TIV2c groups, respectively.

A total of 2333 subjects 4 to < 18 years of age were enrolled in study V130_03, including 1161 in the 4 to < 9 years age group and 1171 in the 9 to <18 years age group. The solicited safety set included 1135 subjects exposed to QIVc, 570 to TIV1c, and 563 to TIV2c, while the unsolicited safety set included 1149 subjects exposed to QIVc, 579 to TIV1c, and 570 to TIV2c.

The total size of QIVc safety database (2680 adults, of which 1334 received QIVc, and 2332 children 4-18YOA, of which 1159 received QIVc) was considered acceptable because the higher HA antigen content of QIVc (60µg) compared to TIVc (45 µg) due to the addition of a fourth strain is considered unlikely to have an impact on the safety profile and it is deemed possible to extrapolate the profile from the adult safety database of the licensed TIVc to QIVc. Consequently, a database of around 1300 adult subjects is acceptable provided no safety signals arise unique to QIVc.

Therefore, the QIVc database of 1334 subjects ≥18 years of age and 1159 subjects 4 to <18 years is supported by the safety data set from TIVc studies.

The demographic and baseline characteristics were generally comparable between vaccine groups in all age ranges. The majority of subjects were Caucasian followed by Black and Hispanic and from a unique geographical location, USA. Similar numbers of subjects were included in the different groups.

Adverse events

In general, the reactogenicity profile of the QIVc and TIVc vaccines in the QIVC studies were similar to what has been previously reported for the licensed TIVc vaccine. Similar rates of solicited events were observed between QIVc and TIVc.

Solicited adverse events in the adult population (≥18 years of age)

Similar rates of solicited events were observed between QIVc and TIVc. However, the percentages of subjects who reported any solicited local AEs were slightly higher in the QIVc group (41.8%) than in the TIV1c group (35.8%) and TIV2c group (36.5%). The most commonly solicited local AE reported was injection site pain (33.6%, 27.8%, and 29.4% in the QIVc, TIV1c, and TIV2c groups, respectively), followed by erythema (12.7%, 11.9%, and 10.3% in the QIVc, TIV1c, and TIV2c groups, respectively).

The percentages of subjects who reported any solicited systemic AEs were similar in the QIVc and TIV1c and TIV2c comparators (28.5%, 28.7%, and 29.3%). The most commonly reported solicited systemic AEs in adults were headache (14.0%, 13.4%, and 13.4%), fatigue (13.5%, 16.3%, and 12.2%) and myalgia (11.8%, 11.9%, and 11.6%). Fever rates (body temperature ≥ 38.0°C) were low and similar across vaccine groups (0.5%, 0.7%, and 0.5%).

The majority of solicited reactions (local and systemic) were mild to moderate in severity. There were a few severe solicited AE in each group, all of them were reported to be below 1% in the QIVc group.

When analysing the data in the group of adults 18 to <65 years and the elderly (≥65 years) separately, the percentages of local and systemic AEs were slightly different. The most common (≥10%) local reactions in adults in the QIVc group were injection-site pain (45.4%), followed by injection-site erythema (13.4%), and induration (11.6%). The most common systemic AEs were headache (18.7%), fatigue (17.8%) and myalgia (15.4%) The most common local reactions in the elderly were injection-site pain (21.6%) and injection-site erythema (11.9%). Systemic reactions were reported below 10% in this age group. These data show that the local and systemic reactions reported in QIVc group tended to be slightly higher in the group of adults (18 to <65 years) than in the group of elderly (≥ 65 years of age). This is similar to what has been observed with TIVc and TIVe comparator vaccines.

In both age groups pain at injection site was reported as very common and the percentage was higher in the QIVc group than in the comparator groups (33.6% in QIVc group vs 27.8% and 29.4% in TIV1c and TIV2c respectively). In the TIVc studies, injections site pain was the only reaction where the risk ratio gave any indication for a higher incidence in the TIVc group compared to the TIVe group. Even that, a higher difference could be observed if an extrapolation between data from QIVc group in V130_01 and pooled exposed safety population from adults TIVc studies had been done, as these reactions were even lower in the TIVc pooled studies. This issue (percentage of subjects with pain at injection site higher in the QIVc group than in the comparator groups) was raised as an OC (Q109). The applicant acknowledges these data but they are not considered a matter of concern regarding safety of QIVC since the reactions were generally mild to moderate in severity.

Solicited adverse events in the paediatric population (4 to < 18 years of age)

The most common solicited local AE in subjects 4 to < 18 years of age in all vaccine groups was injection site pain (reported by 59%, 58%, and 57% of subjects in the QIVc, TIV1c, and TIV2c groups, respectively), and in subjects 4 to < 6 years of age injection site tenderness (55%, 51%, and 48% of subjects in these same vaccine groups). Other common solicited local AEs included injection site erythema (21%, 21%, and 19% in the QIVc, TIV1c, and TIV2c groups, respectively) and injection site induration (16%, 18%, and 14%). Generally, smaller percentages of subjects 4 to < 9 years of age

reported individual solicited local AEs after the second vaccination except injection site tenderness that was reported in higher percentages in subjects 4 to < 6 years of age, and more frequently in the QIVc group when compared with the TIV1c and TIV2c groups.

Most of the solicited local AEs were mild to moderate in severity and had their onset from 6 hours to 2 days after the vaccination. In general, severe local solicited AEs were infrequent and reported in similar percentages across all age and vaccine groups. Severe injection site pain was reported by 1% of subjects in all three vaccine groups, while severe injection site tenderness was reported by 2%, 1%, and 2% of subjects in the QIVc, TIV1c, and TIV2c groups, respectively. Severe erythema and induration were reported by ≤1% of subjects in any vaccine group. In subjects to 9 < 18 years of age there were no severe solicited local AEs experienced by > 1% of subjects within a vaccine group.

The percentages of subjects who reported individual solicited systemic AEs were mostly similar across the QIVc, TIV1c, and TIV2c vaccine groups. Only in the 4 to < 6 years of age group more subjects in the QIVc group experienced a change in eating habits, sleepiness, and irritability than in the TIV1c and TIV2c groups.

Overall, in subjects 4 to < 18 years of age, the most common individual solicited systemic AEs were headache (20%, 20%, and 16% in the QIVc, TIV1c, and TIV2c groups, respectively), fatigue (17%, 17%, and 17%), and myalgia (16%, 17%, and 14%). In subjects 4 to < 6 years of age, the most common individual solicited systemic AEs were sleepiness (21%, 13%, and 14%), irritability (19%, 14%, and 15%), and change in eating habits (14%, 8%, and 7%) in the same vaccine groups. For subjects 6 to < 18 years of age the most common solicited systemic AEs following vaccination were also headache, fatigue, and myalgia.

Solicited systemic AEs classified as severe were infrequent in the paediatric group. Severe AEs that were experienced by > 1% of subjects in a vaccine groups were change in eating habits in the TIV1c group (4%), sleepiness in the TIV1c group (3%), and irritability (2% in the QIVc and TIV1c groups). Fever (≥ 38.0^{o}C) was reported by similar percentages of subjects across vaccine groups (3%, 4%, and 2% in the QIVc, TIV1c, and TIV2c groups, respectively). Only one subject in the group of 9 to < 18 Years of Age reported a body temperature value over 40.0^{o}C in the QIVc group.

Unsolicited Adverse events

The percentage of unsolicited AEs reported in the adult population (Study V130_01) from Day 1 through Day 22, was similar in the QIVc, TIV1c, and TIV2c groups (16.1%, 14.7%, and 16.5%, respectively). These results are comparable to the results reported in the pooled exposed safety population with TIVc. The percentages of AEs judged by the investigator as possibly/probably related to the study vaccine were also similar across the groups (3.9%, 3.1%, and 4.2%, respectively).

Among all subjects ≥18 years of age, all possibly/probably unsolicited AEs sorted by preferred terms were reported below 1%, with the exception of injection site haemorrhage (1.1%) reported in the >65 years age group. No new safety signals were detected.

In subjects 4 to < 18 years of age (from Day 1 to Day 22 and Day 1 to Day 50 for not previously vaccinated subjects), similar percentages of subjects in the QIVc, TIV1c, and TIV2c groups reported unsolicited AEs (24.3%, 24.0%, and 26.7%, respectively). Similar trends for unsolicited AEs reported by ≥1% of subjects were observed in subjects 4 to < 9 years of age and 9 to < 18 years of age. The percentages of AEs judged by the investigator as possibly/probably related to the study vaccine were also similar across the groups (4.9%, 5.9%, and 5.4%, respectively).

In contrast with the adult population, there were more individual unsolicited AEs experienced by > 1% of in subjects 4 to < 18 years of age across all 3 vaccine groups. This was more evident when comparing the adult population with the subjects in the younger age groups (4 to < 6 and 6 to < 9 years of age). A question was raised about this difference and it was noted that different rates of unsolicited adverse events between paediatric and adult populations have been reported in other influenza vaccine studies. In addition, the percentage of AEs judged by the investigator as possibly/probably related to QIVc was similar in the paediatric population (4.9%) as compared to the adult population (3.9%).

The unsolicited AEs represent commonly observed intercurrent illnesses/diagnoses that occur in a paediatric population. There were no noteworthy differences in types of unsolicited AEs between the vaccine groups.

The most commonly reported AEs considered by the investigator to be possibly or probably related to study vaccine were in the SOC of "General disorders and administration site conditions" and were reported by the highest percentages of subjects in the 4 to < 6 years age group (4.3%, 6.5%, and 5.3% in the QIVc, TIV1c, and TIV2c groups, respectively) and by the lowest percentage in subjects 9 to < 18 years of age (2.2%, 2.7%, and 1.8%).

Serious adverse event/deaths/other significant events

SAEs were more commonly reported in the older age group of >65 years than in the 18 to < 65 years group (4.7% to 6.2% of subjects across vaccine groups vs 1.5% to 1.8%). However, none of them were judged as possibly/probably related to study vaccine.

In the paediatric QIVc V130_03 study, the percentage of subjects who reported SAEs throughout the study (day 1 to 181 or 210) were 0.5% (QIVc), 1.2% (TIV1c) and 0.4% (TIV2c). No SAE was judged by the investigator as possibly/ probably related to the study vaccines.

A total of 12 deaths were reported during the entire course of the adults study. No deaths were considered to have a reasonable possibility for causal relationship with the vaccine. They were due to the comorbid conditions commonly observed in the elderly population. No deaths were reported during the entire course of the paediatric study. No reported NOCD was considered related to the study vaccines, across the QIVc adults and paediatric studies.

Laboratory findings

Laboratory safety data were collected for 2 adult TIVc studies (V58P1 and V58P5). No safety-related clinical laboratory data were collected in the other adult TIVc studies or in the paediatric TIVc studies or the adult and paediatric QIVc studies. No changes in laboratory values over this period were considered either vaccine related or clinically meaningful.

Safety in special populations

Data from special groups, such as immunocompromised individuals, pregnant, or breast feeding women have not been analysed, as all of these have been considered as an exclusion criteria in the QIVc studies. During the course of the evaluation procedure data on pregnant women have however been provided, which do not raise any safety concern. A total of 12 pregnancies were reported in the V130_01 study. The description of the AEs during the pregnancies that occurred during study QIVc 130_01 were provided and do not raise any safety concern.

In general, the immunogenicity and safety of QIVc was studied in healthy subjects. Nonetheless, subjects belonging to risk groups for influenza (as people with chronic respiratory diseases, chronic cardiovascular

diseases, chronic metabolic disorders and chronic renal and hepatic diseases) were also enrolled in this trial (no exclusion criteria). Furthermore, some immunocompromised subjects were enrolled. However the data is limited.

Selected unsolicited AES indicating allergic reactions were analysed for the pooled adult and paediatric safety populations from TIVc studies. Data regarding allergic, hypersensitivity or immunological reactions in the QIVc studies has been provided during the application and the results show no significant differences between QIVc and TIV1c/TIV2c treatment groups.

Safety related to drug-drug interactions and other interactions

The study V130_01 was not intended to measure drug interactions. Concomitant administration of QIVc with other vaccines was not assessed, particularly those recommended in elderly such as pneumococcal, and herpes zoster vaccines. Study V58P4E2 in adults 65 years and older to assess the effects of concomitant administration of pneumococcal vaccine with TIVc did not show an impact of concomitant vaccination on the safety of TIVc. Based on these results and on clinical experience with TIVc vaccine, Flucelvax Tetra can be given at the same time as other vaccines, and this is reflected in the SmPC.

Discontinuation due to adverse events

No AEs related to the study vaccine led to discontinuation in the QIVc adults study. However, three paediatric subjects withdrew from the V130_03 study because of AEs probably related to vaccination (prolonged erythema and induration at injection site; pain in extremity and pruritus).

Post marketing experience

TIVc (Optaflu) was granted market authorization in Europe through the centralized procedure in June 2007. The licensure was not renewed for commercial reasons, and therefore expired in June 2017. Flucelvax (US brand name for TIVc) received US FDA marketing authorization on November, 2012. Approval of an extension of Flucelvax (TIVc) to ≥4 years of age was granted by US FDA on May 23, 2016. Post-marketing data for TIVc, representing over 10 million subjects exposed, are available and summarized in the most recent Optaflu Periodic Safety Report n.18 covering the period March 16, 2016 to March 15, 2017. The cumulative analysis concluded that no new or changing safety signals during the reporting interval were evidenced and the benefit/risk assessment was considered to remain favorable (and unchanged).

No new safety events were identified in a post-marketing observational safety study V58_30OB, in which over 4500 persons >18 years of age received the seasonal TIVc (Optaflu) between 2012 and 2015 in a general primary care setting.

QIVc was approved by US FDA on May 23, 2016 as Flucelvax Quadrivalent, for prevention of influenza in children ≥4 years of age via the accelerated approval pathway, with more than 5 million doses distributed for use during the 2016/2017 influenza season. The analysis of post-marketing safety data currently confirms the known safety profile of the product, consistently with the TIVc experience and TIVc and QIVc clinical trial data.

Additional adverse events were reported from post-marketing surveillance. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish, for all events, a causal relationship to vaccine exposure. They included: allergic or immediate hypersensitivity reactions, including anaphylactic shock; generalized skin reactions including pruritus, urticaria or nonspecific rash; extensive swelling of injected limb and paresthesia. These events

are continuous monitored as per QIVc Risk Management Plan. In addition, syncope and pre-syncope have been observed as a vasovagal reaction to injections, as for other vaccines and not specific to QIVc.

Finally, although the overall experience of the use of QIVc and TIVc in pregnant women in clinical studies is limited, there are no safety signals that might put at risk the health of women who were exposed to TIVc during pregnancy. A pregnancy registry (post-approval commitment with the US FDA) was initiated in NH 2017 in the United States and is designed as a prospective observational safety study. The objective is to evaluate pregnancy outcomes as well as major congenital malformations, preterm birth and low birth weight among women immunized as part of routine care with TIVc or QIVc during pregnancy.

The marketing experience is consistent with a favourable safety and tolerability profile of both TIVc and QIVc as demonstrated by the clinical development program.

2.6.1. Discussion on clinical safety

The clinical development program builds on that of the TIVc development, which has demonstrated the safety, immunogenicity and efficacy of TIVc compared to licensed egg-based comparators.

The only relevant difference between the 2 vaccines is the addition of a fourth strain. The HA antigen content of the QIVc is therefore 15 µg higher than that of the TIVc, therefore it is deemed possible to extrapolate the adult and children safety databases of the QIVc from the licensed TIVc.

Safety data from 12 clinical studies performed with TIVc have been provided. These data were pooled into an adult data set (subjects ≥18 years of age) and a paediatric data set (subjects 4 to < 18 years of age). The TIVc clinical program demonstrated that the safety profile of TIVc is similar to that of egg-based comparator trivalent influenza vaccines.

Safety data from 2 clinical studies comparing QIVc with TIVc are included. Both studies (Study V130_01, Study V130_03) were phase 3 trials conducted in the US, in adults 18 years of age and above (including elderly adults), and in subjects 4 to < 18 years of age, respectively. Both studies used 2 trivalent, cell culture-derived vaccines as active comparators (each with a different influenza B strain, TIV1c and TIV2c). Safety data for these 2 studies were provided unpooled. The QIVc database of 1324 subjects ≥18 years of age and 1159 subjects 4 to <18 years is acceptable because no safety signals arose unique to QIVc and it is supported by the safety data set from TIVc studies.

A total of 2680 adults 18 years of age and above were enrolled, including 1340 elderly (≥65 years of age) subjects. Of those 1324 subjects were exposed to QIVc, 673 exposed to TIV1c, and 665 exposed to TIV2c respectively.

A total of 2333 subjects 4 to < 18 years of age were enrolled, including 1161 in the 4 to < 9 years age group and 1171 in the 9 to <18 years age group. Among subjects 4 to < 18 years of age 1149 received at least one dose of QIVc, 579 of TIV1c, and 570 of TIV2c. Among the 1161 children 4 to < 9 years of age 468 received two doses of the QIVc.

The demographic and baseline characteristics were generally comparable between vaccine groups in all age ranges. Similar numbers of subjects were included in the different groups.

A review of the available data indicated that safety and reactogenicity profile of the QIVc was generally comparable to that of the TIVc across all age groups. As found with other inactivated influenza vaccines the reactogenicity of the QIVc and the TIVc was somewhat higher in younger subjects.

In subjects ≥18 years of age the most commonly solicited local AE reported was injection site pain (33.6%, 27.8%, and 29.4% in the QIVc, TIV1c, and TIV2c groups, respectively), followed by erythema

(12.7%, 11.9%, and 10.3% in the QIVc, TIV1c, and TIV2c groups, respectively). As for injection site pain in general the percentage of subjects who reported any solicited local AEs were slightly higher in the QIVc group (41.8%) than in the TIV1c group (35.8%) and TIV2c group (36.5%). However this is not considered a matter of concern regarding safety of QIVC since the majority of solicited reactions were mild to moderate in severity. A few severe solicited AE were reported but all were below 1% in the QIVc group.

When analysing the data in the group of adults ≥65 years separately the most common solicited adverse reactions for QIVc were injection-site pain (21.6%) and injection-site erythema (11.9%); headache, fatigue, myalgia were reported below 10% in this age group.

The percentages of subjects who reported any solicited systemic AEs were similar in the QIVc and TIV1c and TIV2c comparators (28.5%, 28.7%, and 29.3% respectively). The most commonly reported solicited systemic AEs in adults were headache (range 14.0% - 13.4%), fatigue (range 16.3% - 12.2%) and myalgia (range 11.9% - 11.6%). Fever rates (body temperature ≥ 38.0°C) were low and similar across vaccine groups (range 0.7%, 0.5%).

The data show that similar to what has been observed with TIVc and TIVe comparator vaccines the local and systemic reactions reported for the QIVc vaccine tended to be slightly higher in the group of adults 18 to <65 years than in the group of ≥65 years of age.

Within the paediatric population, in subjects 6 <18 years of age the most common solicited local AE in all vaccine groups was injection site pain (reported by 59%, 58%, and 57% of subjects in the QIVc, TIV1c, and TIV2c groups, respectively), and in subjects 4 to <6 years of age injection site tenderness (55%, 51%, and 48% of subjects in the same vaccine groups). Other common solicited local AEs included injection site erythema (21% - 19%) and injection site induration (18% - 14%). Generally, smaller percentages of subjects 4 to <9 years of age reported individual solicited local AEs after the second vaccination except injection site tenderness that was reported in higher percentages in subjects 4 to <6 years of age, and more frequently in the QIVc group when compared with the TIV1c and TIV2c groups. Severe local solicited AEs in QIVc group were rare and reported in similar percentages to TIVc vaccines.

Overall in subjects 4 to <18 years of age, the percentages of subjects who reported individual solicited systemic AEs were generally similar across the QIVc, TIV1c, and TIV2c vaccine groups. However, in the 4 to <6 years of age group more subjects in the QIVc group experienced a change in eating habits, sleepiness, and irritability than in the TIV1c and TIV2c groups (see below).

Altogether in subjects 4 to <18 years of age, the most common individual solicited systemic AEs were headache (20%, 20%, and 16% in the QIVc, TIV1c, and TIV2c groups, respectively), fatigue (17% all groups) and myalgia (16%, 17%, and 14% in the QIVc, TIV1c, and TIV2c groups, respectively).

In the younger age group, 4 to <6 years of age, the most common individual solicited systemic AEs were sleepiness (21%, 13%, and 14% in the QIVc, TIV1c, and TIV2c groups), irritability (19%, 14%, and 15% same order groups), and change in eating habits (14%, 8%, and 7% same order groups).

Solicited systemic AEs classified as severe were infrequent in the paediatric group. Severe AEs that were experienced by >1% of subjects in QIVc vaccine group was irritability (2%). Fever (≥38.0°C) was reported by similar percentages of subjects across vaccine groups (3%, 4%, and 2% in the QIVc, TIV1c, and TIV2c groups, respectively).

The majority of solicited local and systemic reactions following QIVc, TIV1c, and TIV2c vaccination across all age groups were graded as mild or moderate and mostly resolved within 3 days or less.

The percentage of unsolicited AEs reported in the adult population was similar in the QIVc, TIV1c, and TIV2c groups (16.1%, 14.7%, and 16.5%, respectively). These results are comparable to the results reported in the pooled exposed safety population with TIVc. The percentages of AEs judged by the investigator as possibly/probably related to the study vaccine were also similar across the groups (3.9%, 3.1%, and 4.2%, respectively).

Among all subjects ≥18 years of age, all possibly/probably unsolicited AEs sorted by preferred terms were reported below 1%, with the exception of injection site haemorrhage (1.1%) reported in the >65 years age group. No new safety signals were detected.

In subjects 4 to <18 years of age (from Day 1 to Day 22 and Day 1 to Day 50 for not previously vaccinated subjects), similar percentages of subjects in the QIVc, TIV1c, and TIV2c groups reported unsolicited AEs (24.3%, 24.0%, and 26.7%, respectively). The unsolicited AEs represent commonly observed intercurrent illnesses/diagnoses that occur in a paediatric population. Similar trends for unsolicited AEs reported by ≥1% of subjects were observed in subjects 4 to <9 years of age and 9 to <18 years of age. The percentages of AEs judged by the investigator as possibly/probably related to the study vaccine were also similar across the groups (4.9%, 5.9%, and 5.4%, respectively).

The most commonly reported AEs considered by the investigator to be possibly or probably related to study vaccine were in the SOC of "General disorders and administration site conditions", and were reported by the highest percentages of subjects in the 4 to <6 years age group (4.3%, 6.5%, and 5.3% in the QIVc, TIV1c, and TIV2c groups, respectively) and by the lowest percentage in subjects 9 to < 18 years of age (2.2%, 2.7%, and 1.8%).

Additionally, in contrast with the adult population, there were more individual unsolicited AEs experienced by >1% of in subjects 4 to <18 years of age across all 3 vaccine groups. This was more evident when comparing the adult population with the subjects in the younger age groups (4 to <6 and 6 to <9 years of age). It was noted that different rates of unsolicited adverse events between paediatric and adult populations have been reported in other influenza vaccine studies. In addition, the percentage of AEs judged by the investigator as possibly/probably related to QIVc was similar in the paediatric population (4.9%) as compared to the adult population (3.9%).

In order to obtain further insight in AEs indicating allergic reactions in the adult and paediatric QIVc studies, the applicant conducted retrospective analyses of unsolicited AE data from V130_01 and V130_03 using preferred terms from MedDRA SMQ: anaphylactic reactions (broad definition), angioedema (narrow definition), hypersensitivity (narrow definition). Reports of AE including anaphylaxis, angioedema and hypersensitivity were uncommon, particularly within 21 days after vaccination. Cough was the commonly reported AE term during this period, particularly in the paediatric population. However, the vast majority of these cases were not assessed as related to study vaccination by the Investigator. No significant differences were observed between QIVc and TIV1c/TIV2c treatment groups.

In adult population, SAEs were more commonly reported in the older age group of >65 years than in the 18 to <65 years group (4.7% to 6.2% of subjects across vaccine groups vs 1.5% to 1.8%). However, none of them were judged as possibly/probably related to study vaccine.

In the paediatric QIVc 130_03 study, the percentage of subjects who reported SAEs throughout the study were 0.5%, (QIVc), 1.2% (TIV1c) and 0.4% (TIV2c). No SAE was judged by the investigator as possibly/ probably related to the study vaccines.

The 12 deaths reported in the adults study were not considered to have a reasonable possibility for causal relationship with the vaccine, but were due to the comorbid conditions commonly observed in the elderly

population. No deaths were reported during the entire course of the paediatric study. No reported NOCD was considered related to the study vaccines, across the QIVc adults and paediatric studies.

No AE related to the study vaccine led to discontinuation in QIVc adults study. However, three paediatric subjects withdrew from the study because of AEs probably related to vaccination (prolonged erythema and induration at injection site; pain in extremity; and pruritus), the AEs were not severe in nature.

Safety in special populations (immunocompromised individuals, pregnant, breast feeding women or subjects with an increased risk of influenza associated complications) has not been investigated. All of these have been considered as exclusion criteria in the QIVc study and this is included as missing information. However, a total of 12 pregnancies were reported in the adults QIVc V130_01 study. The description of the AEs during the pregnancies that occurred during study QIVc 130_01 does not raise any safety concern. In addition, a prospective observational safety study to evaluate pre-specified outcomes among women immunized as part of routine care with TIVc or QIVc during pregnancy is ongoing. Concerning the missing information, vaccine effectiveness studies will be conducted yearly in the context of the DRIVE consortium in Europe and the applicant will submit these data for assessment regularly. This is included in the RMP and should provide relevant information about the efficacy of the vaccine during routine use in special population.

Study V58P15 investigated the safety and tolerability of TIVc in children and adolescents 3 to <18 years of age and at risk for influenza related complications. Results of the study demonstrated that vaccination with TIVc or TIVeA (comparator), administered as either 1 or 2 IM doses, was well tolerated in children and adolescents 3 to <18 years of age considered at risk for influenza-related complications. A comparable safety profile in this special population can be expected from the QIVc vaccine.

In summary, the QIVc studies demonstrated that addition of a fourth strain does not alter the safety profile of QIVc, which remains similar to that of TIVc. Similar rates of solicited events were observed between QIVc and TIVc. Similar rates of unsolicited AEs judged by the investigator as possibly/probably were observed between QIVc and TIVc and no new safety signals were detected. No SAEs, NOCD and deaths in paediatric and adult populations were judged by the investigator as possibly/ probably related to the study vaccines.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on clinical safety

After review of the submitted data collected in the 2 phase III studies it can be expected that the QIVc safety profile is in general comparable to that of the TIVc licensed comparators. No new safety signal was seen in the submitted clinical database. It can be concluded that the increase in antigen amount due to the additional B strain does not have any clinically relevant impact on the safety of the vaccine. The safety profile of QIV is considered positive, provided that the outstanding safety data from ongoing study V130_12, which include subjects from 2 to <18 years of age do not reveal any safety signal.

The safety profile of QIV is considered adequate to support the proposed indication for prophylaxis of influenza in persons of 9 years of age and older.

There is limited data in immunocompromised patients, in subjects with underlying diseases and regarding the use in pregnant and breastfeeding women. These populations will be followed post-authorisation.

A pregnancy registry to evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunized as part of routine care with

the seasonal cell culture influenza trivalent (TIVc) or quadrivalent (QIVc) vaccine during pregnancy will be set up as indicated in the RMP.

2.7. Risk Management Plan

Safety concerns

Important identified risks	None
Important potential risks	Neuritis
	Convulsion
	Encephalitis (ADEM)
	Vasculitis
	Guillain-Barré Syndrome
	Demyelination
	Bell's palsy
	Immune thrombocytopenia
Important missing information	Safety in immunocompromised patients
	Safety in subjects with underlying diseases
	Use in pregnant and breastfeeding women

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 – Required additional pharmacovigilance activities				
Pregnancy Registry – V130_110B	Evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunized as part of routine care with the seasonal cell culture influenza trivalent (TIVc) or quadrivalent (QIVc) vaccine during pregnancy.	Major congenital malformations in new-borns, preterm birth and low birth weight outcomes	Final report	31 December 2021
A non-interventional study of vaccine effectiveness; QIVc versus no vaccination in persons 9 years and older (DRIVE sub-analysis).	To perform an analysis of influenza vaccine effectiveness of QIVc vaccination versus no vaccination in persons 9 years and older		Planned for the 2019-20 influenza season.	First annual submission of results 31 December 2020 and annually thereafter

In addition, an annual Enhanced Passive Safety Surveillance system will be put in place for the product.

Risk minimisation measures

Safety concern	Routine risk minimization measures	Pharmacovigilance activities
Important identified risks: None		
Important potential risks:		
Neuritis	None	EPSS: Enhanced Passive Safety Surveillance
Convulsion	None	EPSS: Enhanced Passive Safety Surveillance
Encephalitis (ADEM)	None	EPSS: Enhanced Passive Safety Surveillance
Vasculitis	None	EPSS: Enhanced Passive Safety Surveillance
Guillain-Barré Syndrome	None	EPSS: Enhanced Passive Safety Surveillance
Demyelination:	None	EPSS: Enhanced Passive Safety Surveillance
Bell's palsy	None	EPSS: Enhanced Passive Safety Surveillance
Immune thrombocytopenia	None	EPSS: Enhanced Passive Safety Surveillance
Missing information		
Safety in immunocompromised patients	In SmPC warning and precaution section 4.4 the following is stated: Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.	EPSS: Enhanced Passive Safety Surveillance
Safety in subjects with underlying diseases	In SmPC warning and precaution section 4.4 the following is stated: Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.	EPSS: Enhanced Passive Safety Surveillance
Use in pregnant/breastfeeding women	**In SmPC section 4.6 Fertility, Pregnancy and Breast-feeding the following is stated:** Pregnancy Healthcare providers should assess the benefit and potential risks of administering the vaccine to pregnant women taking into consideration official recommendations. The safety of QIVc in pregnancy has not been assessed in clinical trials. There are no reproductive and developmental toxicology studies with QIVc. Reproductive and developmental toxicology data from cell-based trivalent influenza vaccine (TIVc) do not predict an increased risk of developmental abnormalities (see section 5.3). Breast-feeding QIVc has not been evaluated in nursing mothers.	A Pregnancy Registry (V130_110B) to evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunized as part of routine care with the seasonal cell culture quadrivalent (QIVc) vaccine during pregnancy is ongoing. EPSS: Enhanced Passive Safety Surveillance

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested harmonisation of the PSUR cycle with the Data Lock Point (DLP) of the other influenza vaccines administered i.m., using 15 March 2019 as the first DLP.

2.9. New Active Substance

Not applicable

2.10. Significance paediatric studies

The CHMP is of the opinion that study V58P12, which is contained in the agreed Paediatric Investigation Plan P/0341/2017 and has been completed after 26 January 2007, is considered as significant.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.11.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Flucelvax Tetra (Influenza vaccine (surface antigen, inactivated, prepared in cell cultures)) is included in the additional monitoring list as it is a biological product that is authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Influenza is a highly infectious acute respiratory disease of global importance that occurs in epidemics throughout the Northern Hemisphere and Southern Hemisphere winter months. Worldwide, annual influenza epidemics, throughout the world, result in about 90 million cases with approximately 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths, of which 28,000 to 111,500 occur in children.

Influenza A and B viruses are important human respiratory pathogens which are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people, but occasionally also through contact with virus contaminated fomites. Both A and B viruses cause seasonal influenza epidemics and out of season sporadic cases and outbreaks. Influenza occurs globally with an annual attack rate estimated at 5%– 10% in adults and 20%–30% in children. More severe illness is more common in the elderly, the very young and those with other chronic medical conditions.

Although human influenza A viruses are perceived to carry greater risk because they account for the majority of influenza cases in most seasons, influenza B viruses also impose a substantial public health burden, particularly among children and at-risk subjects. Specifically, the type B influenza virus causes 20% to 25% of influenza infections worldwide. In addition, since the 2001-2002 influenza season, both influenza B lineages, B/Victoria-like viruses and B/Yamagata-like viruses, have co-circulated in Europe.

3.1.2. Available therapies and unmet medical need

The most effective single public health intervention to mitigate and prevent seasonal influenza is vaccination. Available antiviral treatments (NA inhibitors) are limited and have limited efficacy, in addition to generating a high rate of drug-resistant viruses. Only symptomatic treatment is otherwise available.

Annual prophylactic vaccination is the most effective way to prevent disease and severe outcomes. Influenza vaccines are designed to protect against illness from the circulating virus strains, and the most commonly used vaccines have been inactivated influenza vaccines.

For many years, seasonal influenza vaccines included antigens from 3 influenza strains in their composition, 2 influenza A strains (largely A/H1N1 and A/H3N2), and a strain from 1 of the 2 influenza B lineages (B/Yamagata or B/Victoria). However, TIVs have been associated with potential for vaccine mismatch depending on whether B/Yamagata or B/Victoria is chosen for inclusion in the seasonal vaccine. Indeed, the predicted B strain included in the recommended northern hemisphere seasonal influenza vaccine was incorrect during 5 of 10 influenza seasons from 2001/2002 to 2010/2011. In order to avoid vaccine mismatch, quadrivalent influenza vaccines that include influenza B strains from both lineages have been recommended and these are expected to provide protection against the additional B strain. A US study estimated that, in a season with a B strain mismatch, availability of quadrivalent influenza virus vaccines could reduce annual influenza cases (range: 2200–970,000), hospitalizations (range: 14–8200), and deaths (range: 1–485) in the US.

Flucelvax Tetra is a quadrivalent inactivated influenza vaccine including B strains of both lineages and is therefore expected to improve protection in target populations, especially in children where significant disease due to influenza B strains occurs. Other quadrivalent influenza vaccines are authorised for use in adults and children both at the national and at the centralised level in Europe. Nevertheless it is important

to have different products authorised, also considering that this vaccine is prepared in cell culture differently to others, which may constitute an alternative for people allergic to eggs.

3.1.3. Main clinical studies

The clinical development program of QIVc includes two-phase III stratified, randomized, double-blind, multicentre studies that were conducted to evaluate the safety and efficacy (immunogenicity) of the QIVc in children and adolescent (4 to < 18 years of age, V130_03 clinical study) and in adults (18 to > 75 years of age, V130_01 clinical study). In these studies, 2 different comparator vaccines were used: TIV1c (cell-based, trivalent influenza virus that included the B strain from the B/Yamagata lineage) and TIV2c (cell-based, trivalent influenza virus vaccine that included the B strain from the B/Victoria lineage).

In addition to these studies, supportive data from 16 phase I to III studies have been performed with TIVc (Optaflu was authorised in Europe via the centralised procedure in 2007), including 12 randomized controlled studies against an egg-based licensed comparator, of which the most relevant for this application are the absolute efficacy study in adults 18 to <50 years (V58P13) and the immunogenicity and safety study in children 4 to <18 years (V58P12).

3.2. Favourable effects

The clinical development program was based on the assumption that Flucelvax Tetra, based on the same manufacturing platform as TIVc (Optaflu/Flucelvax), is as safe and would induce similar protection against influenza disease as demonstrated in prior studies with TIVc, with the additional benefit of protecting against both influenza B lineages.

Efficacy was measured in terms of immunogenicity data. Flucelvax Tetra elicited antibody responses in both adults and children that are highly likely associated with protection against influenza. The results in both Flucelvax Tetra studies were evaluated using the haemagglutination inhibition (HI) assay. The two co-primary immunogenicity objectives (non-inferiority criteria as assessed by the ratio of GMTs and differences in seroconversion rates) were achieved for all 4 influenza strains, indicating non-inferiority of Flucelvax Tetra over the previously licensed TIV1c (Optaflu) for the 3 influenza strains (A/H1N1, A/H3N2 and B1) and TIV2c vaccine for B2 influenza strain. Moreover, the secondary endpoint aimed at showing superiority of Flucelvax Tetra over TIV1c and TIV2c in antibody response to unmatched B strains as assessed by the ratio of GMTs and differences in seroconversion rates, was also achieved.

Immunogenicity analysis in subpopulations, taking into account the age, sex, race/ethnicity, baseline serostatus and previous vaccination status, did not show any important difference between the TIVc and Flucelvax Tetra within the different subgroups analysed.

In conclusion, the immunogenicity results have demonstrated that the addition of a 4th influenza strain to the formulation does not impact the immunogenicity of the other 3 influenza strains included in the Optaflu vaccine. Therefore, non-interference has been proven. Moreover, taking into account the immune response to the additional B strain present in QIVc, it is expected that QIVc provides additional benefits in terms of clinical protection against this B strain.

Additional important data was provided from the supportive studies conducted with TIVc (V58P13 in adults and V58P12 in children). Study V58P13 showed that TIVc is able to induce an overall absolute efficacy of 83.8% against matched strains and 69.5% against any strains, numerically higher that the efficacy seen in the same trial with the egg based influenza vaccine comparator. Immune responses induced by TIVc in children and adolescents >9 YOA in study V58P12 were found to be generally

comparable or higher (depending on the strain) to those induced by TIVe in the same trial and age group and to those induced in adults in study V58P13, where efficacy was demonstrated.

3.3. Uncertainties and limitations about favourable effects

No clinical efficacy data were generated with Flucelvax Tetra, as efficacy was measured in terms of immunogenicity (HI titres). However this is acceptable as immunobridging is satisfactory based on robust levels of antibodies similar to TIVc for which efficacy was demonstrated. Vaccine performance will be followed up post-authorisation in effectiveness studies.

Virus neutralization and anti-NA data were not generated in the TIVc/QIVc studies assessed for this application. Neutralising antibodies will however be assessed in the ongoing study V130_12 and in the two planned QIVc studies V130_10 and V130_14 (6 months to < 48 months), and this is considered acceptable.

Cell-mediated immunity (CMI) was also not investigated. An evaluation of CMI may have been particularly informative in the elderly due to known effects of immuno-senescence and observations that high HI titres may not predict protection. Although it is acknowledged that these studies were performed before the new influenza vaccine guideline was adopted, this remains a limitation of the dossier.

Concomitant administration of QIVc with other vaccines was not assessed, particularly those recommended in elderly such as pneumococcal (conjugate and not conjugate), and herpes zoster vaccines. However based on data generated with TIVc in coadministration with a pneumococcal vaccine in elderly and based on the understanding of lack of interference with TIVc and many vaccines coadministered, it is reasonable to assume that Flucelvax Tetra can be coadministered with other vaccines.

Two other limitations that affect all influenza vaccines are:

- The efficacy depends on the degree of antigenic match between vaccine and circulating strains and therefore the efficacy of the seasonal influenza vaccines could vary in different seasons.
- In general, all influenza vaccines, including Flucelvax Tetra, show reduced efficacy (in terms of immunogenicity) in the elderly due to immune senescence. However, the immunogenicity results obtained with Flucelvax Tetra in subjects >75 years of age were similar with results obtained with the authorised TIVc vaccines in this age group, indicating similar acceptable levels of efficacy.

Effectiveness studies will be conducted yearly and should be able to generate useful data to monitor the performance of the vaccines over time and in special population subgroups during routine use.

An efficacy study is ongoing in children from 2 to 18 YOA and will be useful to provide confirmatory data in younger children in support of the immunogenicity data evaluated in this application.

3.4. Unfavourable effects

In both, children and adults (>18 years of age), similar rates of solicited events (local and systemic) were observed between Flucelvax Tetra and TIVc, and the majority of solicited reactions were mild to moderate in severity.

The most commonly reported (≥10%) reactions in subjects who received Flucelvax Tetra were pain at the injection site (34%), headache (14%), fatigue (14%), myalgia (14%), erythema (13%) and induration (10%). The incidence of some adverse reactions was considerably lower among subjects ≥65 years of age when compared to subjects 18 to < 65 years of age.

The most common (≥10%) adverse reactions reported in paediatric subjects of 9 to <18 years of age were injection site pain (58%), headache (22%), erythema (19%), fatigue (18%), myalgia (16%), and induration (15%). Similar rates of local and system adverse reactions were reported in the overall paediatric population 4 to <18 years of age. Compared to adults 18 years of age and older, paediatric subjects generally reported higher rates of local and systemic adverse reactions.

No severe adverse events and deaths in paediatric and adult populations were judged by the investigator as possibly/ probably related to the study vaccines.

It is important to highlight that the overall safety profile of Flucelvax Tetra was comparable to that of the comparator cell-based trivalent influenza vaccines. Thus, the available data demonstrated that the addition of a fourth strain does not alter the safety profile of Flucelvax Tetra vs. the previously licensed TIVc, which remains favourable, similarly to that of TIVc in subjects from 9 years of age. No new safety signals were detected.

3.5. Uncertainties and limitations about unfavourable effects

Safety in special populations (immunocompromised individuals, pregnant, breast feeding women or paediatric subjects with an increased risk of influenza associated complications) has not been specifically evaluated. This data will be gathered post-authorisation by means of effectiveness studies.

For ethical reasons pregnant women are currently excluded from clinical trials. Therefore, no clinical study in pregnant women was performed with Flucelvax Tetra. However, a prospective observational safety study is ongoing to evaluate pre-specified outcomes among women immunized as part of routine care with Flucelvax Tetra during pregnancy. These data shall be provided post-authorisation.

3.6. Benefit-risk assessment

Overall, Flucelvax Tetra clinical studies indicated similar immunogenicity as compared to the previously licensed TIVc vaccine (Optaflu) in subjects from 9 YOA. For subjects older ≥18 YOA, data from clinical efficacy studies with Optaflu (TIVc) and a TIV grown in eggs support the adequate efficacy of Flucelvax Tetra.

An important uncertainty is that there are no clinical efficacy data with Flucelvax Tetra, as efficacy was measured in terms of immunogenicity (HI titres). However, regarding adults (≥18 years of age), the applicant has clinical efficacy data with Optaflu (TIVc) from study V58P13, which assessed the clinical efficacy of Optaflu (TIVc) versus placebo in terms of protection against illness caused by virus-confirmed community-acquired influenza wild type strains. Data from study V58P13 demonstrated high vaccine efficacy of TIVc. Since the immunogenicity results obtained from study V58P13 were similar to the immunogenicity results obtained with Flucelvax Tetra in the same age groups and seasons, it is considered that the absolute efficacy data obtained with TIVc could be extrapolated to Flucelvax Tetra, and therefore additional clinical efficacy data for subjects ≥18 years of age are not considered needed.

Regarding children and adolescents (9 to <18 years of age), the results from trial V58P12, in which a Trivalent Inactivated Vaccine grown in eggs (TIVf) was compared to TIVc grown in cell culture, show a robust immunogenicity of TIVc. Extrapolation of Flucelvax Tetra efficacy for this population is acceptably based on indirect immunobridging to adults aged 18-45 years in whom the efficacy of TIVc was demonstrated. HI titres in study V58P12 in this age subset were generally higher than HI titres seen in adults in the efficacy study V58P13, except for titres against the B strains, for which the immune responses could be viewed as comparable between age groups if the known HI variability is taken into account. Overall the data available for this population indicate that similar clinical protection as seen in

young adults is to be expected. Therefore, it was considered that the available data support use of Flucelvax Tetra from 9 YOA.

In terms of safety, the studies demonstrated that addition of a fourth strain does not alter the safety profile of Flucelvax Tetra, which remains favourable throughout the age range of the indication and similar to that of the previously authorised TIVc. Similar rates of solicited events were observed between Flucelvax Tetra and TIVc, which is found acceptable.

In conclusion the benefit/risk balance for Flucelvax Tetra is considered positive and supports the use of the vaccine for prevention of influenza in individuals 9 years of age and above.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Flucelvax Tetra is favourable in the following indication:

Prophylaxis of influenza in adults and children from 9 years of age. Flucelvax Tetra should be used in accordance with official recommendations.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0341/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0341/2017 have been completed after the entry into force of that Regulation.