17 October 2024
EMA/511525/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Flucelvax

International non-proprietary name: influenza vaccine (surface antigen, inactivated, prepared in cell cultures)

Procedure No. EMEA/H/C/006532/0000

Note

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

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List of abbreviations

ACIP Advisory Committee on Immunization Practices

AE Adverse event

AS active substance

BPL beta-propiolactone

CBER Center for Biologics Evaluation and Research

CHMP Committee for Medicinal Products for Human Use

CI Confidence interval

CMO Contract manufacturing organization

CPP Critical process parameter

CPV continuous process verification

CSR Clinical study report

CT Clinical trial

CTAB cetyl trimethylammonium bromide

CVV candidate vaccine viruses

EMA European Medicines Agency

EU European Union

FAS Full analysis set

FCC Flu cell culture

FDA Food and Drug Administration

FP finished product

GCP Good Clinical Practice

GMP Good Manufacturing 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

IPC in-process control

MAA Marketing Authorization Application

MCB Master cell bank

MDCK Madin Darby Canine Kidney

NA Neuraminidase

NVD Novartis Vaccines and Diagnostics

NOCD New onset of chronic disease

PACMP post-approval change management protocol

PBS phosphate buffered saline

PDL population doubling limit

PFS pre-filled syringe

PP polypropylene

PPQ process performance qualification

PPS Per protocol set

PRTC plastic rigid tip cap

PS80 polysorbate 80

QIV Quadrivalent influenza vaccine

QIVc Quadrivalent influenza virus vaccine (surface antigen, inactivated, cell-based) or Flucelvax Tetra

QP Qualified person

qPCR quantitative polymerase chain reaction

RH relative humidity

SA Scientific advice

SAE Serious adverse event

SCR Seroconversion rate

SD Standard deviation

SOC System organ class

SRD single radial (immune)diffusion

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)

TSE	Transmissible spongiform encephalopathies
UK	United Kingdom
US	United States of America
WCB	Working cell bank
WHO	World Health Organization
WSV	working seed virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Seqirus Netherlands B.V. submitted on 3 June 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Flucelvax, 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 March 2024.

The applicant applied for the following indication:

"Prophylaxis of influenza in adults and children from 2 years of age.

Flucelvax should be used in accordance with official recommendations".

1.2. Legal basis, dossier content

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 tests or studies.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0181/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0181/2024 was completed.

The PDCO issued an opinion on compliance for the PIP P/0181/2024.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Sol Ruiz Co-Rapporteur: Jean-Michel Race

The application was received by the EMA on	3 June 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 September 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2024
The Rapporteurs circulated the Joint Assessment Report to all CHMP members on	10 October 2024
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 on	17 October 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Influenza is a highly contagious infectious disease, characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, cough, sore throat, and rhinitis. Seasonal epidemics occur predominantly during the winter months in the Northern and Southern hemispheres. 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 more frequent and more pronounced in children.

The influenza virus is an orthomyxovirus that can be classified into 3 types (A, B, and C), with type A and type B viruses being the most clinically significant. Influenza type A viruses can be further divided into subtypes based on the hemagglutinin (HA) and neuraminidase (NA) surface glycoprotein antigens, of which the A/H1N1 and A/H3N2 subtypes are the most clinically important for the annual influenza disease burden. Influenza type B viruses are classified into 2 distinct genetic lineages, Yamagata and Victoria; however, the B/Yamagata lineage has not been confirmed to be in circulation since March 2020.

2.1.2. Epidemiology, risk factors and 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.

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.

Seasonal influenza can be prevented by active immunisation. Vaccines are updated routinely with new vaccines developed to match circulating influenza strains. Annual vaccination is recommended to protect against influenza for people at high risk of influenza complications, their carers and health workers.

Other methods of prevention include indirect prevention measures that aims at interrupting or reducing the spread of influenza viruses (transmission barriers, isolation and hygienic measures).

2.1.3. Aetiology and pathogenesis

The influenza virus is an orthomyxovirus that can be classified into 3 biologically similar, but antigenically different types that are known to infect and cause disease in humans, 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.

Type A viruses are associated with both annual epidemics and pandemics, and B viruses contribute to annual epidemics (WHO 2018). The type A viruses are further divided into different subtypes, of which the A/H3N2 and A/H1N1 viruses are the most clinically relevant for the annual influenza disease burden. For influenza B, only a single type is known to exist, but 2 distinct genetic lineages are identified: Yamagata and Victoria (CDC 2017). However, the B/Yamagata lineage has not been confirmed to be in circulation since March 2020 (Paget 2022).

2.1.4. Clinical presentation, diagnosis

Clinical manifestation of influenza virus infection is characterized by an abrupt onset of nonspecific respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis. Influenza is generally self-limited and an uncomplicated disease. It can, however, be associated with severe morbidity and mortality in healthy children and certain groups of children and adults who are at increased risk of severe or complicated illness from influenza. Complications such as febrile convulsions, croup, acute otitis media, lower respiratory infections and encephalitis may arise in children as a consequence of the primary influenza infection, or as a result of secondary bacterial infections. In older adults, pulmonary complications of influenza are most common and include secondary bacterial infection. Among others, acute respiratory infections can exacerbate asthma and chronic obstructive pulmonary disease or lead to decompensation of patients with congestive heart failure or diabetes mellitus and subsequently lead to an increased risk of myocardial infarction and cerebrovascular accident.

Most cases of human influenza are clinically diagnosed. During periods of low influenza activity or outside of epidemics situations, the infection of other respiratory viruses (e.g. SARS-CoV-2, rhinovirus, respiratory syncytial virus, parainfluenza and adenovirus) can also present as influenza-like illness (ILI), which makes the clinical differentiation of influenza from other pathogens difficult. Collection of appropriate respiratory samples and the application of a laboratory diagnostic test is required to establish a definitive diagnosis. Laboratory confirmation is commonly performed using direct antigen detection, virus isolation, or detection of influenza-specific RNA by reverse transcriptase-polymerase chain reaction (RT-PCR). Rapid diagnostic tests are used in clinical settings, but they have lower sensitivity compared to RT-PCR methods and their reliability depends largely on the conditions under which they are used.

2.1.5. 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.

Currently, different seasonal inactivated (split virion, surface antigen) or recombinant influenza vaccines are authorised for children aged 6 months and older, adolescents or adults, as well as a live attenuated influenza vaccine for children and adolescents from 2 years to 17 years of age.

2.2. About the product

Flucelvax is a trivalent surface antigen, inactivated, influenza vaccine, prepared in MDCK cell cultures. The active substance comprises virus surface antigens (hemagglutinin and neuraminidase) of the 3 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 (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.

Flucelvax 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 TIVc consists of a sterile suspension for intramuscular injection containing approximately 15 µg HA from each of the 3 influenza strains (A/H1N1, A/H3N2, and B strain from Victoria lineage; 45 µg in total).

The cell-based production process of "on demand" suspensions of cells does not require medium supplements, 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. Flucelvax is produced using the same cell culture manufacturing platform as Flucelvax Tetra.

Based on global surveillance for actively circulating influenza viruses, there have been no confirmed detection of circulating, naturally occurring B/Yamagata strain since March 2020. Reports of B/Yamagata detections after March 2020 with available samples were identified as the B/Yamagata lineage component of live attenuated vaccines.

Due to the lack of naturally occurring B/Yamagata virus circulation since the last 3 years, the relevance of vaccinating against this lineage is being questioned globally.

In September 2023, the World Health Organization (WHO) issued a recommendation stating that "*inclusion of a B/Yamagata lineage antigen in quadrivalent influenza vaccines is no longer warranted, and every effort should be made to exclude this component as soon as possible*".

In March 2024, the Emergency Task Force (ETF) issued a statement stating that "*antigens of the B/Yamagata lineage should be removed from the live attenuated influenza vaccines ideally for the 2024/2025 influenza season. For all other influenza vaccines, the target for completing the transition to trivalent formulations is the 2025/2026 influenza season*".

In order to follow the above WHO recommendation and ETF statement a new marketing authorisation is applied for Flucelvax (trivalent).

2.3. Quality aspects

2.3.1. Introduction

Flucelvax (TIVc) is a trivalent seasonal inactivated influenza vaccine prepared in cell cultures, containing, as active substance (AS), influenza virus surface antigens (haemagglutinin, HA and neuraminidase, NA) of 3 influenza strains (Type A/H1N1, Type A/H3N2 and Type B/Victoria Lineage), as recommended annually by the World Health Organization (WHO) for the Northern Hemisphere and the EU recommendation for seasonal influenza vaccines.

The vaccine is provided in a pre-filled syringe containing a single dose of 0.5 mL sterile suspension for injection. Each dose of TIVc contains a nominal total of 45 µg of antigens per 0.5ml dose; 15 µg of HA from each of the recommended A/H1N1, A/H3N2, and B/Victoria strains.

Other ingredients are phosphate buffered saline (PBS) pH 7.2, consisting of sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate and potassium dihydrogen phosphate; and water for injection. All are compendial excipients.

The composition of the TIVc finished product (FP) is equivalent to that of Flucelvax Tetra (QIVc), except for the deletion of the B/Yamagata antigen.

QIVc has been licensed in the EU since 2018 and now, following WHO and EU recommendations, the antigens of the B/Yamagata strain are removed from the vaccine composition resulting in this new Marketing Authorization Application (MAA) for TIVc.

Regarding the pre-filled syringe medical device, Seqirus requested a waiver for the Notified Body Opinion with the justification that there are no changes in terms of design, safety and performance characteristics, intended use, usability, and instructions for use vis a vis the medical device used in the previously authorized quadrivalent vaccine, Flucelvax Tetra. In agreement with the European Commission, the Notified Body Opinion waiver was accepted in this exceptional case.

2.3.2. Active substance

2.3.2.1. General Information

The AS consists of three monovalent bulks of purified virus antigens of influenza strains, Type A (H1N1), Type A (H3N2) and Type B (Victoria Lineage). The virus strains are chosen in compliance with the official annual strain recommendation from the WHO and the CHMP and produced in suspension cultures of Madin Darby Canine Kidney (MDCK) cells.

2.3.2.2. Manufacture, process controls and characterisation

Manufacturer(s)

The three ASs are produced by Seqirus, Inc. Holly Springs. A QP declaration concerning GMP compliance by Seqirus Holly Springs is provided.

Description of manufacturing process and process controls

The AS is designated as the Flu Cell Culture (FCC) monovalent bulk.

Each FCC monovalent bulk is prepared by propagation of influenza working seed virus (WSV) in MDCK 33016 protein free (PF) cell suspension cultures (upstream infectious manufacturing process). Following virus propagation, the virus/cell harvest is centrifuged and filtered to remove cells and cell debris.

The active substance is prepared by propagation of influenza working seed virus in MDCK cell suspension culture. The active substance manufacturing process is divided into an upstream process and a downstream process. 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. The downstream process consists of several steps designed to purify whole influenza virus from the clarified virus harvest, inactivate the virus, and then to purify and concentrate the viral surface proteins, haemagglutinin and neuraminidase. In the downstream manufacturing process, clarified harvest is purified and buffer exchanged by chromatography and filtration and the virus concentrate is inactivated. Next, viral surface antigens are preferentially solubilised with the detergent followed by separation of the 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.

There are certain manufacturing steps within the AS process that require tailoring as per the specific viral strain being used, specifically virus propagation and CTAB splitting and adsorption.

Control of materials

Seed viruses: The candidate vaccine viruses (CVV) for the preparation of the WSV lots are obtained from the WHO Collaborating Centers and do not require release testing. The certificate obtained from the supplier is used to release the material. The manufacturing process and control strategy for producing virus seed stocks is described and is acceptable. Seeds generated will be approved by the WHO.

The working seed virus manufacturing process as well as the in-process control and release testing of the WSV are included and considered acceptable.

Cell Substrates: The qualification of the MDCK (Madin Darby Canine Kidney) cells 33016 PF master and working cell banks has been done including adventitious agents testing according to the current regulatory guidelines and is found acceptable. The use of MDCK cell substrate as a starting material is not associated with any elevated risk for oncogenic or tumorigenic potential in the final vaccine product. The studies were conducted according to state-of-the-art knowledge and technology and are found adequate. This is acceptable.

After several derivations of the MDCK33016 cell line, the MDCK 33016 subline was further adapted to serum-free conditions in 1995 and finally adapted to protein-free growth in 1996.

MDCK cells 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 in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate. All filters, membranes and resins are free from animal-derived materials.

Control of critical steps and intermediates

The AS manufacturing control strategy is described. The critical process parameters (CPP) associated with the manufacturing process are provided as well as the in-process controls (IPCs) and the release criteria of the product intermediates and final AS. All 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 per the AS Process Validation Master Plan. The process validation plan was executed for each monovalent bulk, at the production scale Multiple runs were executed for the A/H3N2 strain (A/South Australia/55/2014) and batches each were produced for the other two strains. The data confirmed that the process can reproducibly manufacture material that meets acceptance criteria.

The manufacturing process for virus seeds is considered validated as there were no changes with respect to that already approved Flucelvax Tetra.

Regarding the annual activities that the applicant plans to undertake to support the annual strain variation, these include infection bioreactor optimization and splitting optimization. This is acceptable.

In conclusion, the data presented in section 3.2.S.2.5 are deemed sufficient and acceptable.

Manufacturing process development

The applicant has also provided an overview of the technical transfer and all process changes implemented since the initial manufacturing process. Comparability analysis has been performed to demonstrate that the different batches produced are comparable.

Basic research on cell culture-based production methods were initiated in Marburg, Germany. The first manufacturing runs in small scale fermenter systems began in 1992. Formal process development was initiated in October of 1995. Over the period of development, the production facility operated under Behring Vaccine GmbH & Co followed by Chiron Behring GmbH & Co KG (Chiron Vaccines) and then Novartis Vaccines and Diagnostics (NV&D/Novartis Vaccines).

Material for a non-clinical toxicity study in rabbits and for Phase I/II trivalent influenza vaccine (TIVc) clinical trial use was successfully produced on a pilot scale manufacturing process. The scale-up was completed in 2003. Material for clinical lot-to-lot consistency for the Phase III study was successfully produced under GMP conditions using Process 1.0.

Since the manufacture of the Phase III clinical lots with TIVc using Process 1.0, several process improvements to enhance the robustness of the AS manufacturing process were introduced. These improvements were incorporated into the commercial process, which is referred to as Process 1.1. A summary of the changes is provided.

Material for Phase III clinical lots used in a US efficacy study, as well as for quadrivalent influenza vaccine (QIVc) clinical studies, was successfully produced under GMP conditions in 2011 and 2013, respectively, using Process 1.1.

The manufacturing process (Process 1.1) was validated in Marburg and licensed for Flucelvax (trivalent seasonal) in the United States and Optaflu (trivalent seasonal) in Europe and Australia.

The influenza cell culture vaccine monovalent bulk production process (Process 1.1) was transferred from NV&D Marburg, Germany to Seqirus (formerly NV&D) Holly Springs, NC, USA in 2013. The process was licensed on Holly Springs Line 1 in by the US FDA as an additional site for the manufacture of FCC vaccine monovalent bulk. Line 2 at the Seqirus Holly Springs, NC, USA site was subsequently validated and licensed in by the US FDA for the production of FCC vaccine monovalent bulk using Process 1.1.

To improve process yields and overall process robustness, Seqirus developed a next generation active substance manufacturing process, referred to hereafter as Process 3.0. This process has successfully been validated at commercial-scale.

Characterization

Viral HA and NA are the active ingredients in influenza subunit vaccines. The presence of HA is confirmed in both the AS and FP via appropriate activity and quantity by single radial immunodiffusion (SRD). The presence of NA is confirmed in the AS by an identity test based on comparison to international reference standards. The basic integrity of the FCC-derived vaccine antigens has been confirmed in non-clinical and clinical efficacy trials.

Detailed analyses of the physicochemical and biological properties of the FCC-derived HA proteins was conducted. A number of physicochemical studies were also conducted with the NA proteins. The applicant states that minor differences in HA protein structure and characteristics are attributed to the antigen origin (egg versus cell culture). The characterization tests included physicochemical properties, biological activity, and antigen purity.

Characterization of the main vaccine components (HA and NA antigens) has not been conducted in the context of this MAA. However, the applicant refers to data previously generated in comparison to the same antigens present in Agrippal, an equivalent flu vaccine produced in eggs with a very similar virus splitting process. Differences observed in the main antigen component (HA) are not unexpected given the different production systems. These differences concerned mainly glycosylation and did not result in relevant differences in biological (immunogenic) activity. No further characterization studies are considered necessary.

Impurities

Potential process-related impurities have been adequately identified and removal has been described. he most important impurities are residuals from the cell substrate: intact MDCK cells, DNA from host cells and host-cell proteins. e. Overall, consistent clearance is obtained through process evaluation and/or validation.

No product-related impurities have been identified. The applicant states that higher order oligomers of HA are present and are the preferred presentation in influenza vaccine as they elicit a stronger immunogenic response. The applicant concludes that no other product-related impurities are present in the monovalent bulk.

2.3.2.3. Specification

Specification

The specification includes appropriate tests for physicochemical attributes, purity, identity and potency.

Specification methods for the AS are the same as formerly approved for QIVc. The proposed acceptance criteria are properly justified and deemed acceptable.

Analytical methods

Analytical methods used for AS release testing have been described in detail and are all properly validated in accordance with ICH guidelines.

Single radial immunodiffusion (SRD) is used to determine the hemagglutinin (HA) concentration (titre) in AS and FP. The sample being assayed is treated with a zwitterionic detergent which allows the diffusion of antigens into an agarose gel containing either homologous or heterologous antiserum. In reference antiserum, the antigens will form a precipitation ring which is then visualized using Coomassie Blue staining. The diameter of the precipitation ring is then compared with those obtained using dilutions of known standard reference antigen in order to determine HA titre, using the parallel line association method.

Batch analysis

Batch analysis data for 13 batches of the active substance (monovalent bulk representative for the three strains) with bulk batch sizes PPQ/commercial scale batches, manufactured by Process 3) were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference Standards or Materials

Reference standards have not changed from the already approved ones for the QIVc vaccine. The strain-specific reference standards for the HA and NA antigens and antisera are provided by the applicable WHO Collaborating Center for Influenza or ERL.

Container Closure System

The monovalent bulk container consists of a 50-L Nalgene polypropylene (PP) carboy with a stainless-steel dip-tube system integrated into a white polypropylene screwcap closure fitted with a silicone gasket. The information presented on compatibility, integrity and suitability is considered adequate.

2.3.2.4. Stability

An AS shelf-life of 18 months when stored at 2 - 8°C in the specific containers is claimed.

Analytical methods and acceptance criteria were presented for the stability studies. The criteria are the same as for release.

Real time, real condition stability data on 13 batches of active substance (monovalent bulk) from the commercial manufacturing process stored in Nalgene wide-neck polypropylene copolymer bottles with suspended stainless-steel tubes at 2-8°C for up to 18 months and for up to 6 months under accelerated conditions at 23-27°C/55-65% RH according to the ICH guidelines were provided. AS batches from each of the four strains of the QIVc vaccine (H1N1, H3N2 and B/Victoria and B/Yamagata) were included; these comprise the three strains in the TIVc vaccine. The results are compliant with the specifications.

The stability data support the proposed shelf-life and the supplied post-approval stability protocol and stability commitments are agreed.

The applicant has submitted the final stability reports of the NH 2018-2019, 2019-2020, 2020-2021 2021-2022 and 2022-2023 seasons for the different monovalent bulks.

Stability data for B/Yamagata is included in section 3.2.S.7 as this strain was used for the quadrivalent vaccine.

The proposed AS shelf life of 18 months for storage in the proposed container at 2-8°C is deemed acceptable.

2.3.3. Finished Medicinal Product

2 . 3 . 3 . 1 . Description of the product and Pharmaceutical Development

The composition of the TIVc FP is the same as the previously EU-licensed Flucelvax Tetra (QIVc), except for the elimination of the influenza B/Yamagata strain. The composition of the TIVc 0.5 mL syringe presentation is provided in Table . The vaccine contains predominantly hemagglutinin (HA) and neuraminidase (NA) surface antigens from each of the influenza strains recommended annually by the WHO and EU. The antigens are diluted in a clear, sterile, buffered aqueous solution. The finished product is presented as a clear to slight opalescent suspension for injection, in a Type I glass pre-filled

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

Table - Composition of the TIVc Influenza Vaccine Finished Product

Names of Ingredients	Quantity per dose (0.5 mL/dose)	Quantity per mL	Function	Reference to Standars
Active Ingredients Hemagglutinin (HA) and neuraminidase (NA) antigens from the influenza virus strains which are recommended by the WHO/National Regulatory Authorities for the respective season. • A/H3N2 – A/Darwin/11/2021 • A/H1N1 – A/Georgia/12/2022 CVR-167 • B (Victoria lineage)- B/Singapore/WUH4618/2021	15 µg HA (per strain)[1]	30 µg HA (per strain) [1]	Influenza vaccine	CBER/WHO/NIBSC[2]

[1] The appropriate overage will be included to accommodate manufacturing losses, maintaining the target HA value throughout the shelf life as well as differences due to variability in results between the Seqirus and Essential Regulatory Laboratories (ERL) laboratories.

[2] Or as approved by the relevant ERL.

The vaccine is supplied in a pre-filled single-use syringe ready for use. The primary packaging consists of type I glass syringe with a plunger stopper (bromobutyl rubber), with or without a needle. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The formulation of the finished product includes the following excipients:

1. Phosphate buffered saline (PBS), pH 7.2, also referred to as "Buffer M" (containing sodium chloride, potassium chloride, magnesium chloride hexahydrate, disodium phosphate dihydrate and potassium dihydrogen phosphate); all components comply with the current edition of the USP and Ph. Eur. monographs, as applicable. Water for injection is required for the preparation of the buffer and is therefore described as an excipient. WFI complies with the requirements of the current edition of the USP and Ph. Eur. monographs.

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 finished product is a preservative-free and non-adjuvanted trivalent vaccine.

Pharmaceutical development

Flucelvax tetra FP is approved as a quadrivalent FP with influenza strain subtypes H1N1, H3N2, B/Yamagata and B/Victoria lineage. Based on the recommendation of the WHO, Seqirus modified the manufacturing process for Flucelvax tetra to remove the B/Yamagata strain resulting in a trivalent Flucelvax FP.

All the information provided in Section 3.2.P.2.2.1 Pharmaceutical Development has been previously approved for the tetravalent vaccine.

The monovalent bulk concentrates of the three influenza strains are mixed according to their antigen concentration, as determined by the SRD assay. The concentration per dose meets the specifications described in 3.2.P.5.1 Specifications. The buffer used for dilution is phosphate buffered saline (PBS), pH 7.2. Sterile filtration of the final bulk vaccine is carried out via in-line filtration during the filling operation. The trivalent bulk is stored at 2ºC to 8ºC.

Overages for the HA content may be included for each of the three influenza strains, the amount of which depends on the influenza strain and thus may vary from year to year. The overage accounts for SRD method variability, losses during formulation and filling, as well as losses that may occur over the proposed product shelf life. Overages were also applied to the lots used for Phase III clinical trial studies.

The formulation of the final bulk vaccine product was developed in accordance with European Pharmacopoeia standards. The batches used to perform non-clinical studies and clinical trials were manufactured in Marburg, Germany (formulation) and in Rosia, Italy (fill/finish). Details regarding these batches used to perform non-clinical and clinical trials are provided.

With regards to manufacturing process development, the applicant has included the original information submitted for Flucelvax Tetra MAA. The commercial manufacturing process for TIVc was transferred from Marburg and Rosia to Holly Springs and subsequently the process was extended to include a quadrivalent FP. Comparability exercises were performed and demonstrated that the process design, process performance, and analytical attributes for QIVc and TIVc manufactured at Holly Springs were comparable to the QIVc and TIVc manufactured at Marburg/Rosia. This is acceptable.

Subsequently, in addition to the original Seqirus, Holly Springs, US facility, a new Holly Springs facility was introduced to manufacture QIVc pre-filled syringe (PFS) FP. A new comparability exercise was performed and demonstrated that the new facility has a suitable level of comparability in producing QIVc PFS FP for commercial use.

During the MAA for Flucelvax Tetra, PACMPs were submitted for the addition of CSL Behring GmbH and Rovi JC as filling, inspection and packaging and filling and inspection manufacturing sites respectively and implementing variations subsequently allowed their addition to the MA. Subsequently, Rovi SS has also been included as a filling and inspection site.

Rovi Alcalá de Henares has been added as secondary packaging site.

Container closure system

TIVc is supplied as a single dose in a pre-filled 1 mL Type I glass syringe with a plastic rigid tip cap (PRTC), or in a pre-filled 1 mL Type I glass syringe with staked needle, both closed with a bromobutyl plunger stopper.

For the syringe with PRTC, the primary packaging consists of a BD Hypak SCF 1 mL syringe with a PRTC of rubber formulation FM30 (not made with natural rubber). The syringe and PRTC are manufactured as a Luer-Lok™ syringe.

For the syringe with staked needle, two different types of primary packaging can be used: BD Hypak SCF 1 mL syringe with staked needle (25 G x 1") or OMPI EZ-FILL 1ml STD syringe, 25G 1" 5B, RNS 4800GS.

Different studies were performed to qualify the container closure systems (BD Hypak SCF 1 mL and OMPI EZ-FILL 1ml STD syringes): container closure integrity, leachable and extractable, simulation study and toxicological assessment of leachable data. Results demonstrated that both containers are acceptable to contain the vaccine.

The compatibility of the FP with the container is confirmed by the stability studies.

2.3.3.2. Manufacture of the product and process controls

The finished product is manufactured, controlled and stored by Seqirus Inc (Holly Springs, USA) in accordance with cGMPs. Final release is performed by Seqirus Netherlands B.V. (Amsterdam, Netherlands). Further quality control sites are in Ireland and the Netherlands. Additional CMO sites are are utilized for filling, inspection, and secondary packaging. Appropriate evidence of GMP compliance for all sites has been provided.

For the sites involved in the different steps of the manufacturing process of Flucelvax FP, EMA has revised their current status. For Seqirus UK, the applicant presented evidence of GMP compliance from MHRA. MHRA extended the validity of GMP certificates to December 2024: UK MIA 18532 Insp GMP/IMP 18532/29956-0049[H] | MHRA. This is acceptable. No EU GMP certificate for this site is available in EUDRAGMDP. Updated GMP certificates for Rovi San Sebastian (inspection date 2024-05-30), Rovi Complutense (inspection date 2024-01-17), and Rovi Camarillo (inspection on February 2022) were provided. This is acceptable.

Batch Formula

In production, the HA concentration for each strain varies and is calculated using a local procedure for the determination of the strain-specific blend target.

The batch formula for the TIVc product depends on the hemagglutinin content of the monovalent bulks. The hemagglutinin antigen content of each strain varies from lot to lot. Therefore, based on the HA concentration (potency) of each monovalent bulk, the weight of HA antigen for each of the three strains is calculated and the amount of buffer is adjusted according to a defined quantitative formulation.

This particularity of the influenza vaccines, which formula depends on the potency of each monovalent bulk, is understood.

Overview of the FP manufacturing process

The manufacturing process is well described, and different documents are provided in relation to the formulation process (final bulk vaccine) and the filling of the syringes (filling of final bulk vaccine).

Formulation of the trivalent bulk is carried out at the Holly Springs facility using a closed system in a controlled zone. The PBS buffer (Buffer M) is produced in the Formulation Suite in Holly Springs.

The various components are connected by pre-sterilized, disposable assemblies with connectors, or by steam-in-place piping.

The IPCs and critical process parameters are considered acceptable.

All the process controls described by the applicant are agreed upon and acceptable.

The batch size for formulated bulk was the initial qualification batch size registered and is not shipped to CMOs for fill/finish production activities. As commercial markets increased, alternate CMOs were qualified and registered as fill/finish sites. A larger batch size was registered to support market needs with shipping via a shipping bag for ease of transportation purposes. The final bulk of is transferred to flexible shipping bags for transfer to CMO within the hold time for the formulated bulk in the shipping bag. The smaller batch scale bulks are not shipped to CMO. This is acceptable.

The filling process is performed in four sites listed in the Manufacturers Subsection: Seqirus HS, Rovi SSRR, Rovi JS and CSL. The differences in the filling process between the different sites are described.

The IPCs and critical process parameters are considered acceptable.

There are no process intermediates during the formulation, filling and packaging process.

The FP contains three ASs containing PS80, which is added to the process to prevent purified whole virus preparation from aggregation and to stabilize hydrophobic domains. As it was classified as a process related impurity, PS80 content is included in AS specifications but not in the AS stability protocol; it was not considered as a critical stability attribute as it is not added as an excipient to AS. Regarding the FP, PS80 is still a process related impurity which is not included in the specification with the following justification: with known concentrations in the three ASs and known dilutions factors during the FP process, a maximum content was estimated in the QIV MAA; regarding safety, even if its content is higher than PS80 content when used as excipient in FP, on the basis of the available safety data, and levels of polysorbate 80 in approved products, the applicant claims that the presence of up to 1.5 mg PS80 per 0.5 mL dose of QIVc is not considered to be of toxicological concern, which was deemed acceptable during QIV MAA evaluation. Therefore, the applicant has included information according to the draft document "Information for the package leaflet regarding polysorbates used as excipients in medicinal products for human use" 4 December 2023 EMA/CHMP/190743/2016 in the SmPC under 4.4 Special warnings and precautions for use (i.e. warnings necessary for excipients or residues). "Polysorbate 80: the vaccine may contain up to 1.5 milligrams of polysorbate 80 per dose. Polysorbates may cause allergic reactions. (see section 4.3)" Also it has been mentioned in 2 "Flucelvax may contain traces of beta-propiolactone, cetyltrimethylammonium bromide, and polysorbate 80 (see section 4.3)." This is acceptable.

The inspection, labeling and packaging procedures are all found acceptable.

Process validation and/or evaluation

With regards to the process validation, different exercises have been performed to validate the formulation process at Holly Springs and the syringe filling at the four manufacturing sites. The processes validation exercises were performed previously for the formulation and filling of Flucelvax Tetra for multiple batches.

A risk assessment was conducted to address the impact of removal of the B/Yamagata lineage subtype on the manufacturing process and the validated status of that process. Potential process, validation, and quality related risks associated with removing the B/Yamagata sub-type from the FP were

assessed. Each risk was assessed with respect to the current process and procedural controls in place. Additional required mitigation strategies were identified and documented. The conclusion of the risk assessment is that the removal of the B/Yamagata strain from the QIVc manufacturing process will still maintain the process in its validated state therefore, the validated QIVc manufacturing process will be used to manufacture TIVc. The risk assessment is considered acceptable.

2.3.3.3. Product specification

The specifications for release of TIVc final bulk vaccine and final lot are provided in the dossier.

The summary protocol for the production and testing of TIVc is provided.

The attributes analysed for FP release are considered acceptable. The justification is acknowledged and accepted.

A risk assessment was performed for all direct and indirect product contact components used in the manufacturing processes for the Flu Cell Culture Quadrivalent Influenza Vaccine (Flucelvax_Quadrivalent (QIVc)) Finished Product to determine the potential for N-nitrosamine introduction to the Finished Product (both pre-filled syringes and multi-dose vials).

Risk assessments have been performed for all stages of manufacture for the FCC Quadrivalent Influenza Vaccine. In summary, the risk of nitrosamine impurities manufacturing process of this product is inherently low. The ultrafiltration and diafiltration steps and chromatographic purification step performed in primary manufacturing lead to a minimal risk associated with the AS, as these filtration steps would remove nitrosamine impurities based on their low molecular weight.

Although it is acknowledged that the elemental impurity profile of Flucelvax is expected to be in line with that of the approved product Flucelvax tetra, the applicant will submit a risk assessment of elemental impurities for Flucelvax FP in accordance with the Ph. Eur. monograph on pharmaceutical preparations (2619).

Though a small number of items were deemed to have medium or high risks based on a lack of supplier information or due to having a risk for nitrosable substances/nitrosamines, all items were ultimately justifiably classified as low risk. Anything utilized in the sterile filtration of the monovalent, in bulk manufacture or filling for QIVs, is expected to maintain this low risk because these processes do not utilise nitrosating agents or conditions that are favourable for nitrosation. Additionally, the vaccines are stored in a final container closure that does not present risk from high temperature/low pH.

Analytical procedures and reference standards

Of the analytical procedures used for the release of the final bulk vaccine lots and final lots, three are non-compendial: total DNA content, hemagglutinin antigen and non-hemagglutinin protein.

The total DNA content is determined by qPCR using a commercial kit. SRD is used to determine HA antigen concentration (titre) in filled lot. The quantitative determination of protein content is performed by assessing the total bound nitrogen content in a FCC Final Bulk Vaccine sample via chemiluminescence.

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 were transferred from

the Marburg facility to the Holly Springs facility via an analytical method transfer plan. For the method transfers, all test methodologies remain unchanged.

The method validation (non compendial) or method qualification (compendial) reports for all the sites involved in release testing are included. The analytical methods used have been adequately described and the non-compendial methods were appropriately validated in accordance with ICH guidelines.

A list of reference standards used by the applicant in the different release methods has been provided. Strain-specific reference standards for the SRD assay are subject to change, as the composition is reviewed every year according to the WHO and EU recommendations.

Batch analysis

The Batch analysis Section (P.5.4) is included. It contains batch analyses of Flucelvax Tetra vaccine. TIVc formulated bulk batch analysis data will be provided as required with the Annual Strain Update. This is acceptable.

Container closure

TIVc is supplied as a single dose in a pre-filled 1 mL Type I glass syringe with a Plastic Rigid Tip Cap (PRTC) or in a pre-filled 1 mL Type I glass syringe with staked needle. Both syringe presentations are closed with a grey Helvoet FM257/2 (not made with natural rubber), bromobutyl plunger stopper.

For the syringe with PRTC, the primary packaging consists of a BD Hypak SCF 1 mL syringe with a PRTC of rubber formulation FM30 (not made with natural rubber).

For the syringe with staked needle, two primary packaging can be used: BD Hypak SCF 1 mL syringe with staked needle (25 G x 1") or OMPI EZ-FILL 1ml STD syringe, 25G 1" 5B, RNS 4800GS.

The information provided on the components of the containers closure systems are considered acceptable.

2.3.3.4. Stability of the product

The applicant claims a TIVc FP shelf-life of 12 months at 2-8°C, when the product is stored in 1 ml Luer lock syringe with a plastic ridge tip cap (PRTC) overseal and protected from light.

It is acknowledged that TIVc FP has the same formulation as QIVc with the exception that the trivalent product does not contain the B/Yamagata strain. The stability data on which this shelf-life is based are provided, and the studies were according to the ICH guidelines. Final stability reports from different Northern Hemisphere (NH) influenza seasons have been submitted (NH 2019-2020, 2020-2021, 2021-2022 and 2022-2023). Stability data have been submitted for Flucelvax Tetra packaged in the different container closure systems approved and filled in the different manufacturing sites. Based on these available stability data, the shelf life and storage conditions as stated in the SmPC are acceptable.

Stability data for storage conditions at 23-27 C/55-65% RH for up to 6 months were provided for QIVc lots and showed that the QIVc FP is stable for up to 6 months at this storage condition. Based on these data (accelerated conditions), it appears that the final vaccine remains relatively stable or shows only minimal loss of potency for at least a limited period of time. Therefore, the applicant is requested to, via a future variation to this product, provide guidance for users in section 6.4 of the SmPC (in line with EMA guideline EMA/CHMP/BWP/133540/2017), more particularly that short, accidental, temporary

temperature excursions at room temperature (25°C) do not impact the vaccine's quality [Recommendation 001].

In Section P.8.2 it is stated that a minimum of 3 production batches will be tested at the recommended storage condition of 2-8°C for a minimum of 12 months. These three batches are determined based on actual production with a minimum of at least 1 batch from each fill/finish site (if manufactured that year) entered into the stability program according to GMP requirements. This is accepted.

A TIVc FP shelf-life of 12 months at 2-8°C is agreed, when the product is stored in the proposed container and protected from light.

2.3.3.5. Adventitious agents

The adventitious agent management program for the FCC vaccine reflects the ICH recommended complementary approach to controlling potential viral contamination of biotechnology products. The MDCK cell line and other raw materials, including media components, have 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 (influenza, herpes simplex virus 2, murine leukemia virus, reovirus type 3, SV-40 and porcine parvovirus). 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 FCC vaccine manufacturing process is "able to eliminate substantially more virus than is estimated to be present in a single-dose equivalent of unprocessed bulk" (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. This applies to both candidate vaccine viruses, egg-derived and cell-derived.

With regard to media components used for the cell banks, the use of human- and animal-derived media components has been extensively investigated and their TSE-associated risk is found to be negligible. No human or animal derived materials are used in the active substance manufacturing process

The information provided in this Section is considered acceptable.

A risk assessment reviewing the new and emerging adventitious agents potentially affecting Flucelvax TIVc is provided.

2.3.3.6. Post approval change management protocol(s)

The applicant had included the Post Approval Change Management Protocols (PACMPs) submitted as part of the MAA for QIVc. Upon request, these were removed from the TIVc MAA and the relevant information was included in the corresponding CDT sections.

2.3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

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

The TIVc FP is equivalent in composition to the QIVc FP (Flucelvax tetra), which has been licensed in the EU since 2018 except for the elimination of the B/Yamagata antigen. Before the QIVc approval, a trivalent version of the vaccine (Optaflu) was licensed in the EU since 2007 until 2017.

Other than the elimination of the B/Yamagata antigen, there were no changes in the manufacturing process between the established commercial QIVc FP and the new TIVc FP. Thus, the assessment of the manufacture and control of the AS and FP have been straightforward.

Nevertheless, some other concerns were identified, taking into account that TIVc is a stand-alone product, and missing information was identified. These concerns are now solved.

A risk assessment was conducted to address the impact of removal of the B/Yamagata lineage subtype on the manufacturing process and the validated status of that process. The conclusion of the risk assessment is that the removal of the B/Yamagata strain from the QIVc manufacturing process will still maintain the process in its validated state therefore, the validated QIVc manufacturing process will be used to manufacture TIVc. The risk assessment is considered acceptable.

Although it is acknowledged that the elemental impurity profile of Flucelvax is expected to be in line with that of the approved product Flucelvax tetra, the applicant is recommended to submit a risk assessment elemental impurities for Flucelvax FP in accordance with the Ph.Eur. monograph on pharmaceutical preparations (2619),

A recommendation is made to, via a future variation to this product, provide guidance for users in section 6.4 of the SmPC (in line with EMA guideline EMA/CHMP/BWP/133540/2017) on temporary temperature excursions at room temperature (25°C), since stability studies for storage conditions at 23-27 C/55-65% RH for up to 6 months have shown that such excursions do not impact the vaccine's quality.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Flucelvax TIVc is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The applicant has agreed to implement the requested recommendations.

2.3.6. 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:

Recommendation 001: Although it is acknowledged that the elemental impurity profile of Flucelvax is expected to be in line with that of the approved product Flucelvax tetra, the applicant is recommended to submit a risk assessment elemental impurities for Flucelvax FP in accordance with the Ph. Eur. monograph on pharmaceutical preparations (2619)

Recommendation 002: Based on the available stability data (accelerated conditions), it appears that the final vaccine remains relatively stable or shows only minimal loss of potency for at least a limited

period of time. Therefore, the applicant is requested to, via a future variation, provide guidance for users in section 6.4 of the SmPC (in line with EMA guideline EMA/CHMP/BWP/133540/2017), more particularly that short, accidental, temporary temperature excursions at room temperature (25°C) do not impact the vaccine's quality. The following statement could be considered (the applicant should propose and justify a maximum exposure time (hrs/days) at 25°C): "Unopened Flucelvax Vaccine is stable for a total of xx hours/days at 25°C. It is not a recommended storage or shipping condition but may guide decisions for use in case of temporary temperature excursions during the storage at 2-8°C".

2.4. Non-clinical aspects

2.4.1. Introduction

The non-clinical development of the product was focused on demonstration of immunogenicity and efficacy, absence of local and systemic toxicity and reproductive and developmental toxicity. TIVc was immunogenic in mice, rabbits, and ferrets, the animal species used during the non-clinical development. All non-clinical studies are complete at the time of finalizing this report.

The vaccine formulations tested in nonclinical studies were representative of the commercial product or were employed in Phase 3 clinical studies. The animals received the full clinical dose or fractions of the human dose, in a maximized dosing schedule, so that N+1 or N+4 doses were given in the studies.

The proposed therapeutic indication for TIVc (Flucelvax) includes paediatric population. In accordance with current guidelines (WHO Technical Report No. 927, 2005: WHO Guideline on Nonclinical Evaluation of Vaccines) and from a non-clinical perspective, developmental toxicity studies are usually not necessary for vaccines indicated for immunization during childhood. Since the target population might include as well pregnant women and women of childbearing potential, a developmental and reproductive toxicity study was conducted. The results showed TIVc was not a reproductive or developmental toxicant.

The pivotal safety studies were conducted in compliance with GLP. Also, a challenge (efficacy) study was conducted in ferrets in compliance with GLP regulation

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

A justification of the species selection, mouse, rabbit and ferret was not provided. Given the well-known pharmacological properties of the proposed product (TIVc was authorized in the EU in 2007 under the tradename Optaflu (EMEA/H/C/000758) and of similar products (Flucelvax Tetra or QIVc), and having in mind that those species have been recurrently used for the non-clinical development of vaccines, no additional information and justification was requested in this regard from the applicant. The absence of in vitro studies is endorsed.

Overall, the doses used were the full clinical dose (45 µg HA), except in some mice studies where fractions of the dose were used. This is acceptable considering the volume limitations for the administration to small animals and the need to determine the response to different levels of antigen. The dose response study (KOE 090702) clearly showed how the immunogenicity, measured as HI titers, increased with the dose, with very low values when 1/100th of the full clinical dose was employed.

Of importance, the dosing schedule used in all studies (2 or 3 administrations, at least one week apart) exceeded the intended clinical use, where only one shot will be given to the subjects. The selection of ferrets as the animal model for the protection studies, and the need to be primed with heterologous virus is also acceptable. These two points and the age of the animals are aligned with current recommendations (WHO Technical Report No. 927, 2005: WHO Guideline on Nonclinical Evaluation of Vaccines and EMA/CHMP/VWP/457259/2014: Guideline on Influenza Vaccines Non-clinical and Clinical Module).

In the mouse immunogenicity studies, a comparability with egg-derived antigen (Aggripal vaccine), or a combination of the antigens with different adjuvants, or the use of different routes of administration other than IM were also studied. Although in some instances some of those combinations proved to be more efficacious than the current product under assessment, this information is only considered as supportive for the current assessment, given that the scope of this MAA is non-adjuvanted TIVc, administered as a single IM dose. The inclusion of a control arm containing Agrippal was also done in the rabbit and ferret studies and overall, the results were similar between both vaccines.

Several issues identified in the data provided needed further discussion. In mice, a Th2 type-skewed response was observed after vaccination as reported by Vajdy and colleagues and the Wack study, instead of Th1 profile. Secretion of pro-inflammatory cytokines (IL5) and IgG1 isotype was detected, but only mild IFN gamma secretion was evident. However, this type of response is well known when mice from BALB/c background are used to test vaccines (see Charles River Laboratories, strain 028 information), and no further clarification was requested. Another issue relies on the fact that only HI titers have been determined. Although this test is adequate, additional measurements to describe the immunogenic response to the antigens could have been performed; however, given the extensive clinical experience with the product, no additional data were requested and overall, the information provided is deemed sufficient.

In some of the mice studies, and in the GLP-rabbit study, background titers were evident in the control arm against the A/Panama strain and in pre-vaccinated samples from TIVc and Agrippal. The applicant explained this finding as non-specific binding, directly linked to the assay limitations. In any case, a trend towards increasing amounts of A/Panama antibody titre could be seen after the second vaccine dose.

Regarding the efficacy, the study in ferrets demonstrated protection against challenge post vaccination with TIVc. The comparator group was Agrippal, which showed a comparable effect to TIVc. Although some of the parameters tested did not show statistically significant differences between vaccinated and unvaccinated groups (as an example, clinical symptoms during the challenge phase of the study), body weight loss, viral shedding and leukocytes counts (from the nasal washes) were decreased in the TIVc vaccinated animals.

2.4.2.1. Secondary pharmacodynamic studies

No secondary pharmacology studies were conducted due to the nature of the product, which is in accordance with applicable guidelines.

2.4.2.1. Safety pharmacology programme

No dedicated safety pharmacology studies were conducted. This is endorsed due to the nature of the product and the available non-clinical, clinical and post-marketing data with similar adjuvanted vaccines.

2.4.3. Pharmacokinetics

In accordance with current WHO guidelines on non-clinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), pharmacokinetic studies are not required for the vaccine assessment. Since plasma concentrations of antigens are not relevant if an immune response to the antigens is detected, this being considered as an indicator of exposure.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Single-dose toxicity of TIVc, with local tolerability, was addressed after the administration of each dose in the repeat-dose toxicology study in rabbits. Given that two IM were administered to the animals (with a 7-day interval), alternating the site of injection, each limb can be considered as recipient of a "single dose". No remarkable findings were identified after each dose.

2.4.4.2. Repeat dose toxicity

TIVc toxicity was assessed in a repeat-dose GLP study in rabbits, with a total study duration of 3 weeks. The full clinical dose (45 µg HA) was tested. The design is optimized to include a two-week recovery period and as such, the animals received two IM shots of the product, in alternative hind legs, one week apart. The use of the full dose and volume and exceeding the intended number of administrations proposed for annual interpandemic immunization (N+1) is aligned with current guidelines. A positive control arm was included in the study, with the animals receiving Agrippal. The applicant indicates that TIVc lots used in the study were representative of the clinical lots. The number and age of the animals is adequate, as per current guidance (WHO Technical Report No. 927, 2005: WHO Guideline on Nonclinical Evaluation of Vaccines and EMA/CHMP/VWP/457259/2014: Guideline on Influenza Vaccines Non-clinical and Clinical Module).

As described in the Pharmacology section, two doses of TIVc were immunogenic and well tolerated. There were no treatment related adverse effects on clinical observations, ophthalmology, 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. Determination of NOAEL is not relevant, since only one dose has been tested, following current adopted guidelines.

2.4.4.3. Genotoxicity

No genotoxicity studies have been performed in accordance with the WHO Guidelines on Non-clinical Evaluation of Vaccines (2005) and Guidelines on the Non-clinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2014). The absence of these studies is considered acceptable.

2.4.4.4. Carcinogenicity

Standard carcinogenicity studies are not needed, in accordance with current WHO Guideline on Non-clinical Evaluation of Vaccines (2005). However, attending the manufacturing process of TIVc, tumorigenicity has been discussed. TIVc is produced in MDCK cells. Since these cells are known to be

tumorigenic, specific studies were conducted to address that issue. Intact MDCK cells were demonstrated to be tumorigenic, but those are completely removed from the final product. Other intermediates, including MDCK lysates and purified MDCK DNA were not tumorigenic. The data provided sufficiently address this issue and any potential safety concern.

2.4.4.5. Reproductive and developmental toxicity

One GLP reproductive and developmental toxicity study was conducted in female New Zealand White rabbits wherein full human doses of TIVc were administered intramuscularly on premating days 35, 21 and 7, and on gestation days 7 and 20., A phase 3 clinical batch was used in the study and the number of animals was adequate. All rabbits were approximately 7 months old, which is a bit older than expected and might be related to the lower pregnancy rate in some groups. Overall, the study design intended to address stages A through E of the reproductive process (except for determination of effects on estrous cycle), and this is endorsed. As described in the Pharmacology section, TIVc was immunogenic and well tolerated with antibodies being detected even in F1 pups, exposed to the maternal antibodies either in utero or through lactation. Fertility in males was not addressed.

Although the incidences of abortions and mortality were slightly increased in this study, as compared with historical experience, the observations occurred at similar incidences across groups and appeared to be related to spontaneous reductions in feed consumption and associated weight losses, generally after pregnancy was established, and therefore this was not considered to be test article related. No treatment-related effect was observed on female fertility, embryo-fetal development, and post-natal development

Considering the study design and results obtained, women of childbearing potential and pregnant females might be considered for further clinical development, as per current guidelines (WHO Technical Report No. 927, 2005: WHO Guideline on Nonclinical Evaluation of Vaccines and EMA/CHMP/VWP/457259/2014: Guideline on Influenza Vaccines Non-clinical and Clinical Module).

As for children, developmental toxicity studies are usually not required for vaccines intended for immunization during childhood, which together with the results of this study, justified further clinical studies in children.

2.4.4.6. Toxicokinetic data

Considering the nature of the product under assessment, the absence of toxicokinetics, antigenicity, immunotoxicity, dependence, phototoxicity, excipients and metabolites studies is warranted.

2.4.4.7. Local Tolerance

The absence of stand-alone local toxicity studies is endorsed as this was assessed during the repeat dose toxicity study in rabbits. The only notable finding was mild, reversible inflammation seen at the intramuscular injection sites, which is consistent with the administration of an immunogenic vaccine by this route.

2.4.4.8. Other toxicity studies

Regarding impurities, three compounds were identified as warranting a literature-based toxicological evaluation. The maximum amount of each compound (cetyltrimethylammonium bromide, polysorbate 80, and beta-propriolactone) theoretically contained in a vaccine dose poses no risk to the target human populations receiving the product.

2.4.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447100), due to their nature vaccines are unlikely to result in a significant risk to the environment. Therefore, environmental risk assessment studies are not provided in this application for Marketing Authorisation, which is considered acceptable.

2.4.6. Discussion on non-clinical aspects

TIVc vaccine was immunogenic in mice, rabbits, and ferrets. Immunogenicity, expressed as haemagglutination-inhibiting (HI) antibody titers, indicated that TIVc vaccine was comparable to a conventional egg-based vaccine, Agrippal.

Immunogenicity and protection against influenza virus challenge was also demonstrated in the ferret, which is currently considered to be the best animal model for infection with human influenza viruses. TIVc vaccine was immunogenic and was efficacious based on comparisons of effects on bodyweight, body temperature, and leukocyte counts between vaccinated animals and unvaccinated control animals. The TIVc vaccine and Agrippal were generally comparable in ferrets.

In accordance with current WHO guidelines on non-clinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), pharmacokinetic studies are not required for the vaccine assessment. Since plasma concentrations of antigens are not relevant if an immune response to the antigens is detected, this being considered as an indicator of exposure.

In terms of toxicity, the rabbit study addressing repeated dose toxicity as well as local tolerance revealed no concerns regarding the safety of the TIVc vaccine. The only notable finding in the rabbit toxicology study (comparing TIVc vaccine with egg-derived vaccine (Agrippal) was a mild, reversible inflammation seen at the intramuscular injection sites, which is consistent with the administration of an immunogenic vaccine by this route.

Regarding developmental and reproductive toxicity, a study was conducted in female New Zealand White rabbits wherein full human doses of TIVc were administered intramuscularly on premating days 35, 21 and 7, and on gestation days 7 and 20. There was some perinatal maternal mortality (animals euthanized for adverse clinical observations, abortion and total litter loss) in both control and treated groups which was likely related to effects of reduced feed consumption and unrelated to treatment with TIVc. No treatment-related effect was observed on female fertility, embryo-fetal development, and post-natal development. In that study, TIVc was shown to be immunogenic in maternal animals with data suggesting placental and lactational transfer of maternal antibodies to F1 animals.

The absence of any juvenile animal study is acceptable and in line with PDCO decision P/0181/2024.

No mutagenicity or carcinogenicity studies were performed; this is in accordance with the applicable guidelines, WHO Technical Report No. 927, 2005: WHO Guideline on Nonclinical Evaluation of Vaccines and EMA/CHMP/VWP/457259/2014: Guideline on Influenza Vaccines Non-clinical and Clinical Module.

2.4.7. Conclusion on the non-clinical aspects

The non-clinical program is considered complete and acceptable.

2.5. Clinical aspects

2.5.1. Introduction

The clinical development program to support the authorisation of Flucelvax (TIVc) is based on the previous development of TIVc (Optaflu), which was the foundation of development of the quadrivalent version of Flucelvax Tetra (EMEA/H/C/004814/0000) to provide prophylaxis against both Type B-lineages of influenza viruses, B/Victoria and B/Yamagata and on Flucelvax Tetra (QIVc). The initial MAA for Fluvelvax Tetra sought the indication in adults and children from 4 years of age. After the assessment of the clinical studies presented in the QIVc dossier, indication in children from 9 years of age and adults was granted. The indication for Flucelvax Tetra was extended to children from 2 years of age with variation II-13 (EMEA/H/C/004814/II/0013).

No new clinical data have been submitted in this MAA. All relevant clinical studies have been previously submitted and reviewed as part of previous QIV and TIV filings with EMA.

GCP aspects

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 TIVc Studies Included in this Submission

Study country	Objectives	Duration of treatment	Comparator	Study Population	No. of subjects Enrolled (Exposed to TIVc)
Phase III study in healthy subjects					
V58P13 US, Finland, Poland (CSR V58P13)	Safety; efficacy	Single dose, 6-month follow-up	Placebo TIVe (Agrippal) as second investigational vaccine	Healthy subjects 18 to 49 years old.	11404 (3813)
V58P4 Poland (CSR V58P4)	Safety; immunogenicity, non-inferiority	Single dose, 6-month follow-up	TIVe (Agrippal)	Healthy subjects ≥18 years old.	2654 (1330)
V58P4E1 Extension study Poland	Safety; immunogenicity, revaccination	Single dose, 6-month follow-up	TIVe (Agrippal)	Healthy subjects ≥18 years old.	2235 (1105)
V58P9 Lithuania (CSR V58P9)	Safety; immunogenicity, lot to lot consistency	Single dose, 6-month follow-up	TIVe (Agrippal)	Healthy subjects 18 to 60 years old.	1200 (1028)
Phase II in healthy subjects					

Study country	Objectives	Duration of treatment	Comparator	Study Population	No. of subjects Enrolled (Exposed to TIVc)
V58P2 New Zealand (CSR V58P2)	Safety; immunogenicity	Single dose, 3-week follow-up	TIVe (Agrippal)	Healthy subjects ≥18 years old.	223 (110)
V58P5 USA (CSR V58P5)	Safety; immunogenicity, non-inferiority	Single dose, 6-month follow-up	TIVf (Fluvirin)	Healthy subjects 18 to 49 years old.	613 (309)
Phase I/II in healthy subjects					
V58P1 Germany (CSR V58P1)	Safety; immunogenicity	Single dose, 3-week follow-up	TIVe (Agrippal)	Healthy subjects ≥18 years old.	Phase 1: 40 Phase 2: 200 (120)
Post marketing commitment studies					
V58P4E2 Extension study Poland (CSR V58P4E2)	Safety; immunogenicity, revaccination concomitant Pneumococcal polysaccharide vaccine administration	Single dose, 6-month follow-up	TIVe (Agrippal)	Healthy subjects ≥18 years old.	1522 (1108)
V58P12 US and EU (CSR V58P12)	Safety; immunogenicity, non-inferiority	One or two doses, 6-month follow-up	TIVf (Fluvirin)	Healthy subjects 3 to 17 years old.	3604 (2251)
V58P15 Italy, Spain TIVc. (CSR V58P15)	Safety study	One or two doses, 6 month follow up	TIVe (Agrippal)	Subjects at risk for influenza related complications 3 to < 18 years old.	430 (282)
V58_31 Australia, New Zealand, Philippines, Thailand. (CSR V58_31)	Safety study	One or two doses, 6 months follow up	TIVf (Fluvirin)	Healthy subjects 4 to < 18 years old.	2055 (TIVc: 1370)
V58_23 US (CSR V58_23)	Safety; Immunogenicity; Lot to lot consistency study	Single dose, 3-week follow-up	TIVf (Fluvirin)	Healthy subjects 18 to < 49 years old.	1561 (TIVc: 1170)

Table 2 Overview QIVc Clinical Studies Included in this Submission

Study ID	Study Objectives	Study Design	Comparator	Treatment	Study Population	Number of Enrolled Subjects (Exposed)
V130_01 (CSR V130_01)	Noninferior Immunogenicity and Safety	Phase 3, Randomized, Controlled, Double-blind	TIV1c or TIV2c (opposite B-strain)	One dose (0.5 mL)	Healthy subjects ≥18 years old	2680 (QIVc: 1334, TIV1c: 677, TIV2c: 669)
V130_03 (CSR V130_03)	Noninferior Immunogenicity and Safety	Phase 3, Randomized, Controlled, Double-blind	TIV1c or TIV2c (opposite B-strain)	One or two doses (0.5 mL)	Healthy subjects 4 to <18 years old	2333 (QIVc: 1159, TIV1c: 593, TIV2c: 580)
V130_12 (CSR V130_12)	Efficacy, Immunogenicity, and Safety	Phase 3/4, Randomized, Controlled, Observer-blind	Meningococcal (serogroup ACWY) conjugate vaccine	One or two doses (0.5 mL)	Healthy subjects 2 to <18 years old	4514 (QIVc: 2258, MenACWY: 2255)
V130_10 (CSR V130_10)	Noninferior Immunogenicity and Safety	Phase 3, Randomized, Controlled, Observer-blind	QIV	One or two doses (0.5 mL)	Healthy subjects 6 months to <4 years old	2414 (QIVc: 1597, QIV: 805)
Observational Studies with QIVc						
V130_11OB (CSR V130_11OB)	Safety, Registry	Phase 4, Prospective, Observational Cohort / single arm	N/A	One dose (0.5 mL)	Pregnant women, 17 to 45 years old	693*

Source: CSR V130_01, V130_03, V130_12, V130_10, and V130_11OB

Abbreviations: CSR = Clinical Study Report; ID = identification; MenACWY = meningococcal conjugate vaccine; QIVc = Quadrivalent Influenza Cell Culture Subunit Vaccine; TIVc = Trivalent Influenza Cell Culture Subunit Vaccine; TIV1c = Trivalent Influenza Cell Culture Subunit vaccine as constructed to match the WHO recommended influenza strains for 2013/2014 NH season; TIV2c = same A strains as TIV1c but with the influenza B strain from the alternate lineage ("B2" strain); TIVe = egg-based Trivalent Influenza Vaccine; WHO = World Health Organization.

* V130_11OB was a non-interventional study, in which pregnant women were exposed to QIVc through routine prenatal care prior to enrolment in the study.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Pharmacokinetics studies were not conducted for Flucelvax, in line with current guidelines on clinical evaluation of vaccines. 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.

The dosage used in the clinical studies (0.5 mL or approximately 15µg hemagglutinin per influenza strain), the same dose as for planned registration, is similar to that in other inactivated influenza vaccines.

2.5.2.2. Pharmacodynamics

Mechanism of action

Flucelvax provides active immunisation against three influenza virus strains (two A subtypes and one B type) contained in the vaccine by inducing humoral antibodies against the haemagglutinins. 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. At the time most of 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 cited in 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 specified in the protocols of these studies. Neutralizing antibody studies were performed in studies V130_10, V130_12 and V58P16.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetic studies are not required for vaccines and that the pharmacodynamic profile for the vaccine was defined by its immunogenicity profile, as it is detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines".

The hemagglutination inhibition (HI) assay used for immunogenicity evaluation of influenza vaccines, as stated in the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014), is considered adequate for the studies performed. It should be mentioned that HI titers are not a true surrogate marker in the sense that there is not a global accepted clear cut-off titer that defines clinical protection. Nonetheless, it has been widely shown that higher HI titers tend to correlate with better protection.

The dose of 15 µg HA per strain in 0.5 mL for QIVc is in line with the Eur. Ph. requirements and this is the standard dose of all intramuscular inactivated non-adjuvanted influenza vaccines used in the EU.

The use of a single dose in adults and the use of one or two doses, depending on the vaccination history, in paediatric subjects is also endorsed. These schedules are in line with WHO, and CDC, ECDC recommendations and current SmPcs of authorized influenza vaccines. It is noted that the viral strains used in the two studies complied with the annual recommendations made by the WHO at the time the study were performed. This approach is considered adequate.

2.5.4. Conclusions on clinical pharmacology

The CHMP considers that all aspects dealing with clinical pharmacology have been well addressed by the applicant.

2.5.5. Clinical efficacy

Table 3 Overview of TIVc and QIVc Clinical Study Designs

Study No. Countries (No. of Sites) Influenza Season	Study Design (Licensed Control) [assay used for primary immunogenicity objective]	No. of Subjects Enrolled / Completed Protocol	Character-istic and Age of Subjects	Vaccination Schedule (IM doses)	Immunogenicity Objectives
QIVc studies					
V130_01 US (40) 2013-2014	Phase 3, double-blind, randomized, multicenter (Flucelvax, TIV1c) [cell-based HI]	18 to < 65 yrs QIVc 674/639 TIV1c 334/318 TIV2c 332/313 ≥ 65 yrs QIVc 661/646 TIV1c 342/334 TIV2c 337/335	Healthy subjects ≥ 18 yrs	1 vaccination of 0.5 mL (approximately 15 µg HA per strain) QIVc, TIV1c or TIV2c	Noninferiority of QIVc to TIVc Achievement of CBER[a] and CHMP[b] criteria Superiority of antibody response of B1 in QIVc as compared to TIV2c (containing B2) and to B2 strain in QIVc compared with TIV1c (containing B1)
V130_03 US (90) 2013-2014	Phase 3, double-blind, randomized, multicenter (Flucelvax, TIV1c) [cell-based HI]	"not prev. vacc."[c] 4 to < 9 yrs QIVc 340/291 TIV1c 173/153 TIV2c 181/157 "prev. vacc."[d] 4 to < 9 yrs QIVc 235/228 TIV1c 120/117 TIV2c 113/108 9 to < 18 yrs QIVc 584/572 TIV1c 300/290 TIV2c 287/280	Healthy subjects 4 to < 18 yrs	"not prev. vacc."[c] 4 to < 9 yrs 2 vaccinations of 0.5 mL (approximately 15 µg HA per strain) QIVc, TIV1c or TIV2c, 4 weeks apart "prev. vacc."[d] 4 to < 9 yrs, 9 to < 18 yrs 1 vaccination of 0.5 mL (15 µg HA per strain) QIVc, TIV1c or TIV2c	Noninferiority of QIVc to TIVc Achievement of CBER and CHMP criteria Superiority of antibody response of B1 in QIVc as compared to TIV2c (containing B2) and to B2 strain in QIVc compared TIV1c (containing B1)

Study No. Countries (No. of Sites) Influenza Season	Study Design (Licensed Control) [assay used for primary immunogenicity objective]	No. of Subjects Enrolled / Completed Protocol	Character-istic and Age of Subjects	Vaccination Schedule (IM doses)	Immunogenicity Objectives
V130_12 Australia (2), Estonia (5), Finland (10), Lithuania (6), Philippines (7) Poland (6), Spain (1) and Thailand (2) SH 2017, NH 2017/2018, NH 2018/2019	Phase 3/4, randomized, Observer blinded, controlled (Menveo® Meningococcal Conjugate Vaccine) [RT-PCR and viral culture for efficacy objectives; HI and MN assays for immunogenicity objectives]	QIVc: 2258/2249 Comparator: 2256/2247	Healthy subjects age 2 years to < 18 years of age at the time of enrollment	Not previously vaccinated[1] 2 to < 9 yrs: 2 vaccinations of 0.5 mL, 28 days apart Previously vaccinated[1] 2 to < 9 years or 9 to < 18 years: 1 vaccination of 0.5 mL	Absolute vaccine efficacy, immunogenicity, safety
V130_10 US (47) NH 2019/2020	Phase 3, randomized, observer-blind, comparator-controlled, multicenter, noninferiority study (US-licensed QIV: Afluria® Quadrivalent) [HAI and MN assays for immunogenicity objectives using cell-derived and egg-derived target viruses]	QIVc: 1605/1370 US-licensed QIV: 809/710	Healthy subjects 6 months through 47 months of age at the time of enrollment	QIVc: Previously vaccinated: 1 vaccination of 0.5 mL Not previously vaccinated: 2 vaccinations of 0.5 mL US-licensed QIV (Afluria Quadrivalent) following USPI dose recommendations: *6 months through 35 months of age* Previously vaccinated: 1 vaccination of 0.25 mL Not previously vaccinated: 2 vaccinations of 0.25 mL *36 months through 47 months of age* Previously vaccinated: 1 vaccination of 0.5 mL Not previously vaccinated: 2 vaccinations of 0.5 mL	Immunogenicity Safety

Study No. Countries (No. of Sites) Influenza Season	Study Design (Licensed Control) [assay used for primary immunogenicity objective]	No. of Subjects Enrolled / Completed Protocol	Character-istic and Age of Subjects	Vaccination Schedule (IM doses)	Immunogenicity Objectives
TIVc Studies, Adults and Elderly					
V58P13 US (17) Finland (15) Poland (24) 2007-2008	Randomized Observer-blind Phase 3 (Agrippal, TIVeA) [egg-based HI for secondary objective -immunogenicity]	TIVc: 3828/ 3622 TIVeA: 3676/ 3510 Placebo: 3900/ 3712	18 to < 50 yrs	1 vaccination of 0.5 mL (approximately 15 µg HA per strain) TIVc or TIVeA, or 0.5 mL placebo	Vaccine efficacy (Immunogenicity in subset) Achievement of CBER criteria
V58P4 Poland (5) 2004-2005	Randomized Observer-blind Noninferiority Phase 3 (Agrippal, TIVeA) [egg-based HI]	18 to < 60 yrs TIVc: 652/642 TIVeA: 648/634 ≥ 61 yrs TIVc: 678/667 TIVeA: 676/666	Healthy subjects ≥ 18 yrs	1 vaccination of 0.5 mL (approximately 15 µg HA per strain) TIVc or TIVeA	Achievement of CHMP criteria (primary) Noninferiority of TIVc to TIVeA (secondary)
V58P9 Lithuania (2) 2005-2006	Randomized Observer-blind (lot-to-lot consistency) Phase 3 (Agrippal, TIVeA) [egg-based HI]	TIVc: 1029/ 998 TIVeA: 171/168	Healthy subjects 18 to < 61 years of age;	1 vaccination of 0.5 mL (approximately 15 µg HA per strain) TIVc or TIVeA	Lot-to-lot consistency Achievement of CHMP criteria
V58P4E1 Poland (5) 2005-2006	Randomized Observer-blind Phase 3 (Agrippal, TIVeA) [egg-based HI]	18 to < 60 yrs TIVc: 533/530 Control: 534/533 ≥ 61 yrs TIVc: 572/571 Control: 596/594	Healthy subjects ≥ 18 yrs	1 vaccination of 0.5 mL (approximately 15 µg HA per strain) TIVc or TIVeA	immunogenicity, revaccination Achievement of CBER and CHMP criteria
V58P4E2 Poland (5) 2007-2008	Randomized Observer-blind Phase 3 (Agrippal, TIVeA) [egg-based HI]	18 to < 60 yrs TIVc: 549/544 Control: 169/168 ≥ 61 yrs TIVc: 391/389 Control: 144/143	Healthy subjects ≥ 18 yrs	1 vaccination of 0.5 mL (approximately 15 µg HA per strain) TIVc or TIVeA	Concomitant Pneumococcal polysaccharide vaccine Achievement of CHMP criteria
V58_23 US (25) 2014-2015	Randomized, observer blinded Phase 2/3 (Fluvirin, TIVeF) [cell-based HI for TIVc, egg-based HI for TIVeF]	TIVc 1171/ 1147 TIVeF: 390/384	18 to < 49 yrs	1 vaccination of 0.5 mL (approximately 15 µg HA per strain) TIVc or TIVeF	Lot-to-lot consistency Achievement of CBER criteria
TIVc study, pediatric					

Study No. Countries (No. of Sites) Influenza Season	Study Design (Licensed Control) [assay used for primary immunogenicity objective]	No. of Subjects Enrolled / Completed Protocol	Character-istic and Age of Subjects	Vaccination Schedule (IM doses)	Immunogenicity Objectives
V58P12 Finland (14) US (16) Croatia (9) Italy (5) Lithuania (6) Romania (2) Hungary (8) 2007-2008	Randomized Observer-blind Phase 2/3 (Fluvirin, TIVeF) [cell- and egg-based HI]	3 to < 9 yrs TIVc: 1608/1457 TIVeF: 1022/919 9 to < 18 yrs TIVc: 656/643 TIVeF: 318/312	3 to < 18 yrs[e]	Subjects 3 to < 9 years of age received two 0.5 mL injections (approximately 15 µg HA per strain) TIVc or TIVeF 4 weeks apart. Subjects 9 to < 18 years of age received one 0.5 mL injection. (approximately 15 µg HA per strain) TIVc or TIVeF	Noninferiority of TIVc to TIVeF I Achievement of CBER and CHMP criteria

Sources: section 5.3.5.1, CSR V130_01; section 5.3.5.1, CSR V130_03; section 5.3.5.1, CSR V58P4; section 5.3.5.1, CSR V58P4E1; section 5.3.5.1, CSR V58P4E2; section 5.3.5.1, CSR V58P9; section 5.3.5.1, CSR V58P12; section 5.3.5.1, CSR V58P13; section 5.3.5.1, CSR V58_23; section 5.3.5.3 ise-sas 14 APR 2015.
Abbreviations: CBER = Center for Biologics Evaluation and Research; CHMP = Committee for Human Medicinal Products for Human Use; CI = confidence interval; HA = hemagglutinin; HI = hemagglutination inhibition; IM = intramuscular; US = United States; yrs = years of age.
[a] CBER criteria: for adults < 65 years of age and for the pediatric population: The lower bound of the 2-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%, and the lower bound of the 2-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%. For adults ≥ 65 years of age: The lower bound of the 2-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30% and the lower bound of the 2-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60% (Table 2).
[b] Former CHMP criteria: for subjects 18-60 years of age, seroconversions/significant increase in HI titers > 40%, mean geometric increase > 2.5, HI titer ≥ 40 in > 70%. For subjects > 60 years of age, seroconversions/significant increase in HI titers > 30%, mean geometric increase > 2.0, HI titer ≥ 40 in > 60% (Table 2).
[c] Not previously vaccinated: Any child < 9 years of age who did not meet the conditions for "previously vaccinated" (including fewer than 2 doses given since 2010 or receipt of exclusively non-seasonal (pandemic) influenza vaccines), or with unknown influenza vaccination history.
[d] Previously vaccinated: Any child ≥ 9 years of age, and any child < 9 years of age who has received 2 or more doses of seasonal influenza vaccine since July 1, 2010.
[e] Only subjects 4 to < 18 years of age will be presented in sections 2.5 and 2.7.3.

2.5.5.1. Dose response studies

No dose-finding studies were conducted since the vaccine compositions and dosing are in line with the antigen dose of QIVc/TIVc and other seasonal inactivated non-adjuvanted influenza vaccines already authorised.

Vaccine dosage and schedule.

The dose of TIVc has the same antigen content (15 µg HA per strain in 0.5 mL dose) as does QIVc authorised, but does not include the additional 15 µg HA from an influenza B/Yamagata strain.

The schedule is the same as the one approved for QIVc: a single dose for individuals 9 years of age and older, and a two dose-schedule for children less than 9 years of age who have not been previously vaccinated.

Vaccine Formulation

The influenza viral strains used in the vaccines of the clinical trials complied with the annual recommendations made by the WHO at the time the trials were performed and were also the same recommended by the CHMP in the EU.

2.5.5.2. Main studies

The clinical development program includes 4 main studies performed with Flucelvax Tetra (QIVc), and one efficacy study performed with Optaflu (TIVc):

- Two phase III immunogenicity studies comparing QIVc and TIVc in adults (V130_01) and children 4 to 18 years of age (V130_03), assessed as part of the initial MAA of Flucelvax Tetra (QIVc), supporting the initial indication from 9 years of age.
- One phase III/IV efficacy and immunogenicity study in children 2 to 18 years of age (V130_12), assessed as a variation of Flucelvax Tetra (QIVc), supporting an extension of indication in children from 2 years of age.
- One phase III immunogenicity study in children 6 to 47 months of age (V130_10), assessed as a post-authorization measure to Flucelvax Tetra (QIVc).
- One phase III immunogenicity and efficacy study in adults (V58P13) assessed as a post-authorization measure for Optaflu (TIVc)

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 4 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, as well as the stratification by age is appropriate. A significant number of subjects > 75 years old were enrolled.

Subject Characteristics and Main Criteria for Inclusion and Exclusion

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 will 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.

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (e.g., body temperature elevation or use of an excluded medication). Under these circumstances, a subject may be considered eligible for study enrolment if the associated appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

In other words, a subject with an elevated body temperature may be enrolled if the subject meets eligibility criteria and has had a body temperature < 38°C (< 100.4°F) for 3 or more days.

A subject who has received the following medication(s)/vaccine may enrol after the specified window has passed and if the subject continues 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

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.

Objectives

Objectives: The immunogenicity non-inferiority objectives will be evaluated based on haemagglutination inhibition (HI) antibody responses three (3) 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 (4) vaccine strains.
- To demonstrate non-inferiority of antibody responses of QIVc to comparator TIVc1 three (3) 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 (4) vaccine strains separately after vaccination.

The study will be considered a success if both co-primary non-inferiority objectives are achieved.

Key Secondary Immunogenicity Objective:

To evaluate the antibody responses to all four (4) 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-cohorts3.

Secondary Immunogenicity Objectives

- To evaluate the antibody responses to all four (4) 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 (4) 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 (4) influenza strains:
   - Day 22/ Day 1
4. Percentages of subjects achieving seroconversion and HI titre ≥1:40 as calculated for all four (4) 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 have also been 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. Within this study of healthy adult and elderly subjects 18 years to 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 are required.

Table 5 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 6 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 (8) primary hypotheses will be rejected with an overall power of 90% [(0.99^6)*(0.98^2)] and a 1-sided α=0.025, assuming independence.

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 set up.

Statistical methods

Population for Analysis

1. All Enrolled Set: All screened subjects who provided ICF 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" (ie, 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 (ie, 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.

Examples for subjects excluded due to other reasons than major protocol deviations are:

- Subjects who withdrew informed consent
- Subjects with ILI- and RT-PCR-confirmed influenza during the treatment period

Exclusions were considered by objective/time point, ie, 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.

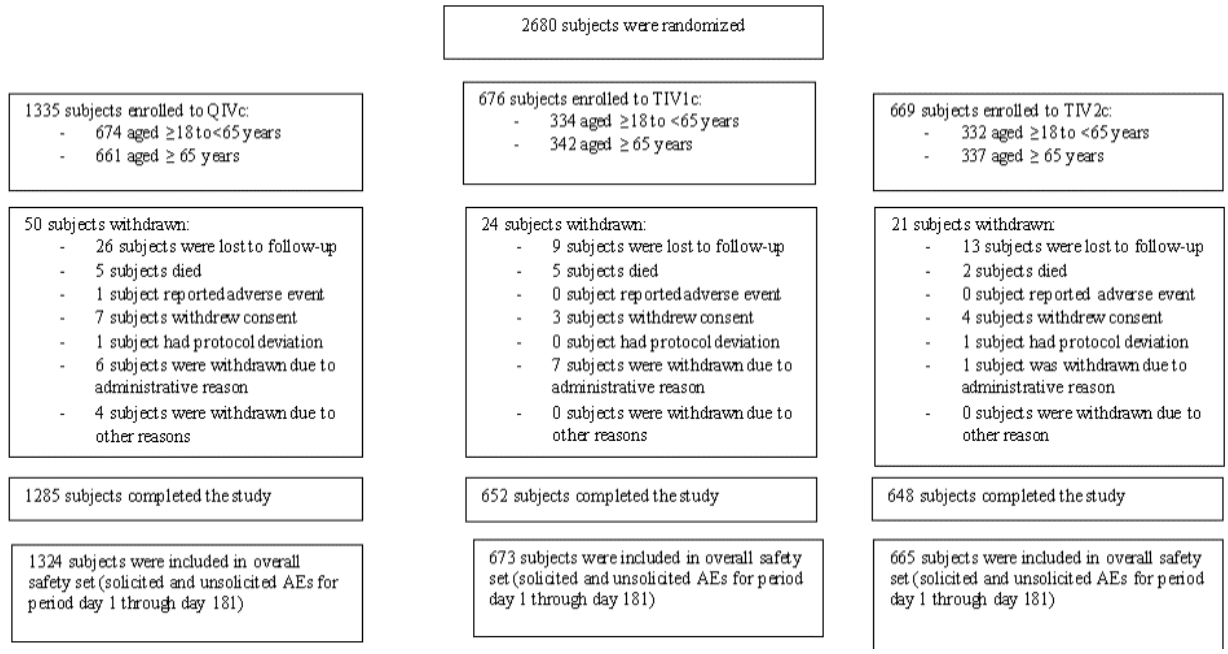
The study was to be declared successful if all primary objectives, i.e., both of the co-primary objectives (associated with 8 hypotheses) were met, so the overall null hypothesis was to be rejected if all 8 single null hypotheses were rejected at 1-sided alpha 0.025. The analysis population for non-inferiority 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, 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 7 number of subjects per age groups

	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)

Sources: section 5.3.5.1, CSR V130_01 Table 14.1.1.3.2 and Table 14.1.1.3.3.1.
Abbreviations: QIVc = cell-based quadrivalent influenza vaccine; TIVc = cell-based trivalent influenza vaccine; PPS = per protocol set. SD = standard deviation.
[a] Race is White, but not of Hispanic or Latino ethnicity.
[b] Race is White, ethnic origin is Hispanic or Latino.

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 past 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 8 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 14.1.1.1.4.
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 10).

- 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) (Table 10).
- 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 remaine 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 10).

Table 9 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/H1 N1	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/H3 N2	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.

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 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 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 10 Immunogenicity Results at 3 Weeks After Vaccination in Subjects ≥ 18 Years of Age, by Age, HI Assay (PPS), Study V130_01

		18 to < 65 Years of Age				≥ 65 Years of Age			
Day 22		QIVc N = 629	TIV1c/TIV 2c[a] N = 309/N = 316	Vaccine Group Ratio[b] (95% CI)	Vaccine Group Difference[c] (95% CI)	QIVc N = 621	TIV1c/TIV 2c[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**)
B/Victoria	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**)
B/Yamagata	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**)

Sources: section 5.3.5.1, CSR V130_01 Table 14.2.1.2.4 and Table 14.2.1.3.4.
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. 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), these results should be interpreted carefully. No clear conclusion can be drawn on the different vaccine efficacy in the different ethnic groups, but in any case they do not represent a problem. The rationale why this does not pose a problem is that the applicant indicated that 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, the applicant argued that 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. The higher immunogenicity response observed for Black and African-Americans would therefore not represent a problem in terms of VE since these data point out to a higher VE for this other population.

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 past CHMP thresholds in both groups. The results of the baseline HI titre analyses are consistent with past influenza exposure in the elderly population as enrolled in study V130_01.

The immunogenicity analysis in subjects with prior exposure to antigen, either from vaccination or exposure to the circulating virus, has a lower likelihood of achieving seroconversion. Subjects who reported prior vaccination should in principle be investigated to determine whether prior vaccination itself affected the immune responses.

In study V130_01, in the PPS for QIVc, the percentage of subjects 18 to < 65 years of age that were not previously vaccinated (80.4%) was higher than the percentage of subjects ≥ 65 years of age not previously vaccinated (70%). For both the TIV1c and TIV2c groups, the percentages of subjects 18 to < 65 years of age previously vaccinated (TIV1c: 21.7%, TIV1c: 20.9%) were lower than the percentages of subjects ≥ 65 years of age previously vaccinated (TIV1c: 29.1%, TIV2c: 29.1%).

Since the rates of prior vaccination were low in this trial related to the timing of study conduct, the applicant appropriately considered that baseline HI titre would be a more objective and reliable indicator of past influenza exposure, hence this analysis was not performed.

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 11 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.

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 13 are required.

Table 12 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

Source: Table 7.4.2.4-1, Protocol version 2, dated 06 May 14.
Sample size estimates are based on V58P12 data (HI Cell -derived Antigen Assay).

Table 13 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

Source: Table 7.4.2.4-2, Protocol version 2, dated 06 May 14.
Sample size estimates are based on V58P12 data (HI Cell -derived Antigen Assay).

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:

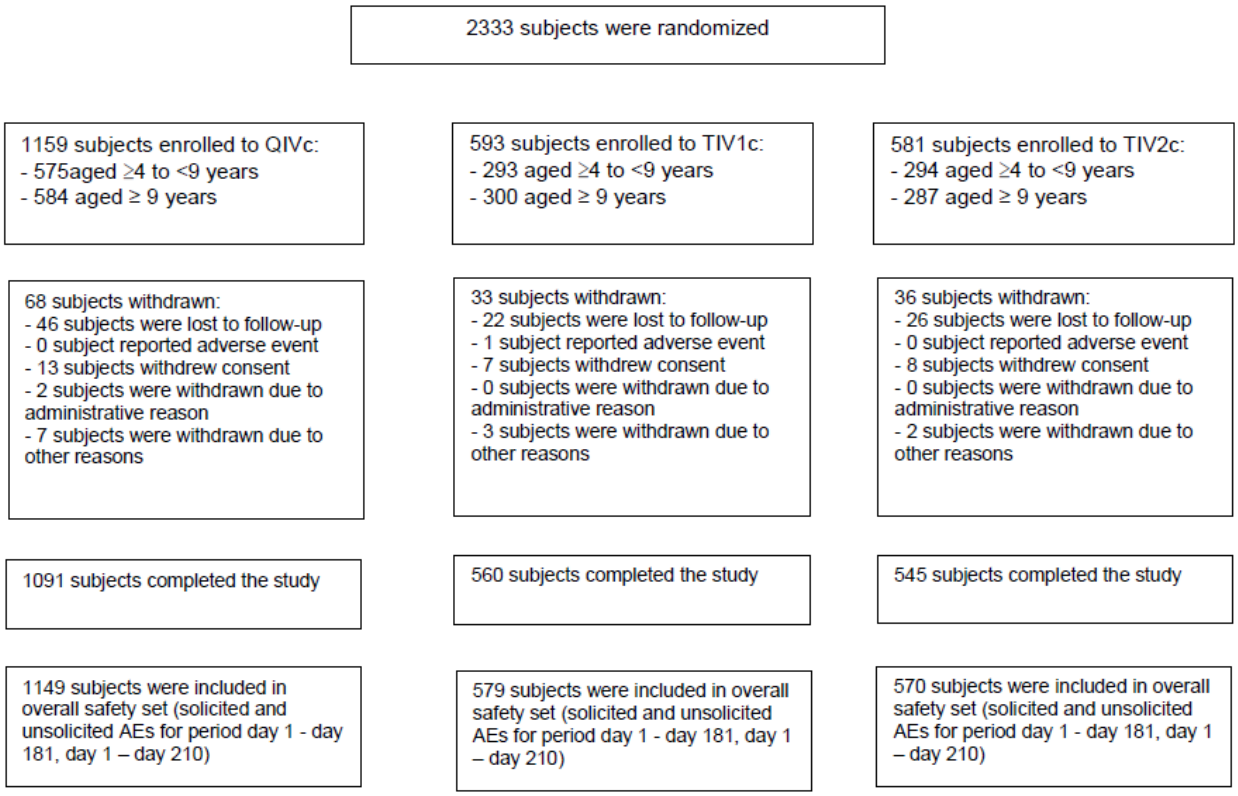
- 1159 subjects in the QIVc group
- 593 subjects in the TIV1c group
- 581 subjects in the TIV2c group

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 14 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 15 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 16 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 16 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 17 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/H1		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 18 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 19 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 than might increase the risk for complications from influenza. Table 20 describes these characteristics for adults and

Table 21 for children.

Table 20 Demographic and Other Baseline Characteristics of Subjects ≥ 18 Years of Age (PPS), Study V130_01

	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
Mean Age in years ±SD	43.0 ±12.82	42.3 ±12.78	42.0 ±12.80	72.3 ±5.49	72.1 ±5.50	72.2 ±5.49	57.5 ±17.67	57.6 ±17.79	57.3 ±17.98
Sex									
Female	342 (54.4)	184 (59.5)	196 (62.0)	347 (55.9)	186 (57.1)	185 (57.3)	689 (55.1)	370 (58.3)	381 (59.6)
Male	287 (45.6)	125 (40.5)	120 (38.0)	274 (44.1)	140 (42.9)	138 (42.7)	561 (44.9)	265 (41.7)	258 (40.4)
Mean Weight in kg ±SD	89.71 ±25.074 N = 628	88.70 ±24.329 N = 308	86.98 ±23.909	83.88 ±19.756 N = 617	83.97 ±18.433 N = 324	84.26 ±19.744 N = 321	86.82 ±22.774 N = 1245	86.28 ±21.622 N = 632	85.61 ±21.935 N = 637
Mean Height in cm ±SD	170.95 ±9.371 N = 628	170.08 ±10.087 N = 308	169.43 ±9.960	167.79 ±10.107 N = 617	167.48 ±10.407 N = 324	167.39 ±10.149 N = 321	169.38 ±9.866 N = 1245	168.75 ±10.326 N = 632	168.40 ±10.100 N = 637
Mean Body Mass Index ±SD	30.67 ±8.199 N = 628	30.53 ±7.496 N = 308	30.32 ±8.153	29.68 ±6.150 N = 617	29.91 ±6.040 N = 324	30.04 ±6.425 N = 321	30.18 ±7.270 N = 1245	30.21 ±6.790 N = 632	30.18 ±7.329 N = 637
Race/Ethnicity									
American Indian	6 (1.0)	5 (1.6)	0 (0.0)	4 (0.6)	2 (0.6)	2 (0.6)	10 (0.8)	7 (1.1)	2 (0.3)
Asian	1 (0.2)	1 (0.3)	2 (0.6)	2 (0.3)	2 (0.6)	1 (0.3)	3 (0.2)	3 (0.5)	3 (0.5)
Black	134 (21.3)	60 (19.4)	60 (19.0)	29 (4.7)	13 (4.0)	13 (4.0)	163 (13.0)	73 (11.5)	73 (11.4)
Caucasian[a]	406 (64.5)	204 (66.0)	222 (70.3)	545 (87.8)	287 (88.0)	284 (87.9)	951 (76.1)	491 (77.3)	506 (79.2)
Hispanic[b]	72 (11.4)	33 (10.7)	29 (9.2)	41 (6.6)	21 (6.4)	21 (6.5)	113 (9.0)	54 (8.5)	50 (7.8)
Native Hawaiian	2 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.2)	0 (0.0)
Other	8 (1.3)	5 (1.6)	3 (0.9)	0 (0.0)	1 (0.3)	2 (0.6)	8 (0.6)	6 (0.9)	5 (0.8)
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)

Sources: section 5.3.5.1, CSR V130_01 Table 14.1.1.3.2 and Table 14.1.1.3.3.1.
Abbreviations: QIVc = cell-based quadrivalent influenza vaccine; TIVc = cell-based trivalent influenza vaccine; PPS = per protocol set. SD = standard deviation.
[a] Race is White, but not of Hispanic or Latino ethnicity.
[b] Race is White, ethnic origin is Hispanic or Latino.

Table 21 Demographic and Other Baseline Characteristics of Subjects 4 to < 18 Years of Age (PPS), Study V130_03

	Number (%) of Subjects								
	4 to < 9 years			9 to < 18 years			4 to < 18 years		
	QIVc N = 467	TIV1c N = 238	TIV2c N = 237	QIVc N = 547	TIV1c N = 272	TIV2c N = 265	QIVc N = 1014	TIV1c N = 510	TIV2c N = 502
Mean age in years ±SD	6.3±1.4	6.2±1.4	6.2±1.5	12.7±2.5	12.7±2.5	12.5±2.4	9.8±3.8	9.7±3.9	9.5±3.7
Sex									
Female	212 (45)	105 (44)	112 (47)	268 (49)	138 (51)	130 (49)	480 (47)	243 (48)	242 (48)
Male	255 (55)	133 (56)	125 (53)	279 (51)	134 (49)	135 (51)	534 (53)	267 (52)	260 (52)
Mean weight in kg ±SD	25.55±7.77	25.77±8.78	25.83±8.06	55.99±21.28	54.94±18.85	54.67±18.57	41.97±22.41	41.32±20.91	40.97±20.48
Mean height in cm ±SD	121.2±10.75	121.3±10.27	122.3±11.67	157.6±14.41	156.6±14.11	156.3±13.34	140.9±22.23	140.1±21.61	140.2±21.14
Body Mass Index	17.1	17.2	17.0	21.9	21.9	22.0	19.7	19.7	19.6
Race/Ethnicity									
American Indian	2 (<1)	1 (<1)	0	2 (<1)	3 (1%)	6 (2)	4 (<1)	4 (<1)	6 (1)
Asian	2 (<1)	1 (<1)	0	4 (<1)	1 (<1)	1 (<1)	6 (<1)	2 (<1)	1 (<1)
Black	112 (24)	61 (26)	57 (24)	110 (20)	44 (16)	45 (17)	222 (22)	105 (21)	102 (20)
Caucasian[a]	328 (70)	167 (70)	166 (70)	414 (76)	211 (78)	206 (78)	548 (54)	284 (56)	266 (53)
Hispanic[b]	104 (22)	51(21)	46 (19)	108 (20)	51 (19)	70 (26)	194 (19)	94 (18)	106 (21)
Native Hawaiian	2 (<1)	1 (<1)	3 (1)	2 (<1)	0	1 (<1)	4 (<1)	1 (<1)	4 (<1)
Other	21 (4)	7 (3)	11 (5)	15 (3)	13 (5)	6 (2)	36 (4)	20 (4)	17 (3)
4 to < 9 Years of Age	-	-	-	-	-	-	467 (46)	238 (47)	237 (47)
Previously Vaccinated	212 (45%)	113 (47%)	98 (41%)	NA	NA	NA	212 (45[c])	113 (47[c])	98 (41[c])
Not Previously Vaccinated	255 (55[c])	125 (53[c])	139 (59[c])	NA	NA	NA	255 (55[c])	125 (53[c])	139 (59[c])

	Number (%) of Subjects								
	4 to < 9 years			9 to < 18 years			4 to < 18 years		
	QIVc N = 467	TIV1c N = 238	TIV2c N = 237	QIVc N = 547	TIV1c N = 272	TIV2c N = 265	QIVc N = 1014	TIV1c N = 510	TIV2c N = 502
9 to < 18 Years of Age	-	-	-	-	-	-	547 (54)	272 (53)	265 (53)

Immunogenicity Results Stratified by age

Table 22 Immunogenicity results across studies in adults 18-64 years of age, 65-75 years /of age, and >75 years of age, by strain (PPS)

V130_01	**Adults 18-64 years**		**Adults 65-75 years**	
	QIVc N=629	TIV1c/TIV2c N=309/316	QIVc N=437	TIV1c/TIV2c N=228/228
A/H1N1				
Baseline GMT (95%CI)	53.3 (46.8; 60.8)	49.8 (41.1; 60.4)	65.6 (58.3; 73.9)	65.0 (55.4; 76.1)
Baseline SPR (95%CI)	64.5% (60.7; 68.3)	64.1% (58.5; 69.4)	76.7% (72.4; 80.5)	74.1% (67.9; 79.7)
Day 22 GMT (95%CI)	472.2 (429.4; 519.2)	432.2 (374.7; 498.5)	201.9 (179.2; 227.4)	210.0 (180.2; 244.8)
GMR (95%CI)	8.9 (7.7; 10.1)	8.7 (7.1; 10.6)	3.1 (2.8; 3.4)	3.2 (2.8; 3.8)
Day 22 SPR (95%CI)	98.6% (97.3; 99.3)	97.1% (94.5; 98.7)	93.4% (90.6; 95.5)	96.5% (93.2; 98.5)
Day 22 SCR (95%CI)	63.3% (59.4; 67.1)	60.2% (54.5; 65.7)	39.4% (34.7; 44.1)	38.2% (31.8; 44.8)
A/H3N2				
Baseline GMT (95%CI)	99.9 (88.3; 113.0)	102.2 (85.1; 122.6)	154.6 (135.8; 176.0)	175.3 (145.1; 200.8)
Baseline SPR (95%CI)	78.1% (74.6; 81.2)	79.9% (75.0; 84.3)	89.9% (86.7; 92.6)	89.0% (84.2; 92.8)
Day 22 GMT (95%CI)	414.1 (379.4; 452.0)	410.5 (361.5; 466.0)	366.8 (329.9; 407.8)	384.6 (328.4; 450.5)
GMR (95%CI)	4.1 (3.7; 4.6)	4.0 (3.4; 4.7)	2.4 (2.1; 2.6)	2.2 (1.9; 2.5)
Day 22 SPR (95%CI)	98.6% (97.3; 99.3)	99.0% (97.2; 99.8)	99.1% (97.7; 99.8)	98.7% (96.2; 99.7)
Day 22 SCR (95%CI)	49.1% (45.2; 53.1)	46.6% (40.9; 52.3)	29.1% (24.8; 33.6)	23.7% (18.3; 29.7)
B1				
Baseline GMT (95%CI)	42.9 (39.1; 47.1)	42.4 (37.2; 48.4)	46.1 (41.8; 50.7)	43.3 (38.0; 49.4)
Baseline SPR (95%CI)	64.1% (60.2; 67.8)	62.5% (56.8; 67.9)	70.9% (66.4; 75.2)	66.7% (60.1; 72.8)
Day 22 GMT (95%CI)	186.6 (171.0; 203.5)	167.7 (149.5; 188.1)	99.7 (90.7; 109.7)	80.6 (71.1; 91.4)
GMR (95%CI)	4.3 (3.9; 4.8)	4.0 (3.4; 4.6)	2.2 (2.0; 2.4)	1.9 (1.7; 2.1)
Day 22 SPR (95%CI)	95.4% (93.4; 96.9)	95.8% (92.9; 97.7)	92.2% (89.3; 94.6)	87.7% (82.7; 91.7)
Day 22 SCR (95%CI)	52.0% (48.0; 56.0)	50.5% (44.8; 56.2)	25.4% (21.4; 29.8)	21.1% (15.9; 26.9)
B2				
Baseline GMT (95%CI)	54.6 (50.3; 59.3)	49.3 (44.2; 56.0)	58.5 (53.4; 64.1)	59.6 (52.0; 68.3)
Baseline SPR (95%CI)	74.6% (71.0; 77.9)	73.4% (68.2; 78.2)	78.9% (74.8; 82.7)	77.6% (71.7; 82.9)

Day 22 GMT (95%CI)	225.9 (208.9; 244.3)	198.4 (176.9; 222.5)	140.0 (127.3; 154.1)	126.0 (110.5; 143.8)
GMR (95%CI)	4.1 (3.7; 4.6)	4.0 (3.5; 4.6)	2.4 (2.2; 2.6)	2.1 (1.9; 2.4)
Day 22 SPR (95%CI)	99.0% (97.9; 99.6)	98.7% (96.8; 99.7)	96.1% (93.8; 97.7)	93.9% (89.9; 96.6)
Day 22 SCR (95%CI)	52.5% (48.5; 56.4)	50.3% (44.7; 56.0)	31.4% (27.0; 35.9)	21.5% (16.3; 27.4)

Source CSR V130_01 Tables 14.2.1.1.4, 14.2.1.2.4, 14.2.1.3.4

Adults > 75 years	**V130_01***		**V58P4****	
	QIVc N=150	TIV1c/TIV2c N=83/82	TIVc N=99	TIVe N=87
A/H1N1				
Baseline GMT (95%CI)	77.3 (64.87; 91.99)	79.3 (59.35; 106.01)	19.2 (15.30; 24.19)	15.1 (11.89; 19.26)
Baseline seropositivity rates (95%CI)	95.33% (90.62; 98.10)	95.18% (88.12; 98.67)	73.74% (63.93; 82.07)	59.77% (48.71; 70.15)
Baseline SPR (95%CI)	84.00% (77.14; 89.47)	78.31% (67.91; 86.61)	32.32% (23.27; 42.47)	32.18% (22.56; 43.06)
Day 22 GMT (95%CI)	173.1 (145.99; 205.27)	189.9 (143.64; 250.98)	101.9 (81.46; 127.38)	81.9 (62.50; 107.41)
GMR (95%CI)	2.24 (1.89; 2.66)	2.39 (1.94; 2.95)	5.29 (4.08; 6.87)	5.41 (3.98; 7.37)
Day 22 SPR (95%CI)	96.00% (91.50; 98.52)	95.18% (88.12; 98.67)	87.88% (79.78; 93.58)	80.46% (70.57; 88.19)
Day 22 SCR (95%CI)	26.00% (19.19; 33.79)	34.94% (24.80; 46.19)	61.62% (51.30; 71.22)	56.32% (45.26; 66.94)
A/H3N2				
Baseline GMT (95%CI)	128.2 (102.89; 159.66)	125.6 (92.77; 170.01)	55.4 (42.32; 72.53)	44.2 (31.33; 62.28)
Baseline seropositivity rates (95%CI)	96.00% (91.50; 98.52)	96.39% (89.80; 99.25)	88.89% (80.99; 94.32)	81.61% (71.86; 89.11)
Baseline SPR (95%CI)	88.0% (81.70; 92.73)	85.54% (76.11; 92.30)	69.70% (59.65; 78.53)	55.17% (44.13; 65.85)
Day 22 GMT (95%CI)	268.5 (218.30; 330.17)	270.8 (207.27; 353.73)	401.8 (315.94; 510.89)	417.9 (326.55; 534.83)
GMR (95%CI)	2.09 (1.80; 2.44)	2.16 (1.77; 2.62)	5.29 (4.08; 6.87)	5.41 (3.98; 7.37)
Day 22 SPR (95%CI)	96.00% (91.50; 98.52)	96.39% (89.80; 99.25)	96.97% (91.40; 99.37)	98.85% (93.76; 99.97)
Day 22 SCR (95%CI)	26.67% (19.78; 34.49)	27.71% (18.45; 38.62)	71.72% (61.78; 80.31)	64.37% (53.38; 74.35)
B1			**B**	
Baseline GMT (95%CI)	54.1 (46.42; 63.14)	47.7 (39.29; 57.83)	17.8 (14.46; 21.95)	12.2 (10.18; 14.63)
Baseline seropositivity rates (95%CI)	97.33% (93.31; 99.27)	98.80% (93.47; 99.97)	72.73% (62.85; 81.20)	62.07% (51.03; 72.26)
Baseline SPR (95%CI)	76.67% (69.07; 83.18)	71.08% (60.09; 80.52)	32.32% (23.27; 42.47)	19.54% (11.81; 29.43)
Day 22 GMT (95%CI)	87.8 (75.11; 102.52)	72.7 (60.30; 87.59)	163.4 (127.27; 209.81)	151.9 (117.23; 196.87)
GMR (95%CI)	1.62 (1.44; 1.83)	1.52 (1.31; 1.77)	9.17 (7.15; 11.76)	12.4 (9.26; 16.74)
Day 22 SPR (95%CI)	92.00% (86.44; 95.80)	87.95% (78.96; 94.07)	89.90% (82.21; 95.05)	89.66% (81.27; 95.16)
Day 22 SCR (95%CI)	9.33% (5.20; 15.16)	15.66% (8.61; 25.29)	83.84% (75.09; 90.47)	82.76% (73.16; 90.02)
B2				
Baseline GMT (95%CI)	83.8 (71.74; 97.83)	93.5 (74.38; 117.65)		
Baseline seropositivity rates (95%CI)	98.00% (94.27; 99.59)	98.78% (93.39; 99.97)		

Baseline SPR (95%CI)	88.00% (81.70; 92.73)	87.80% (78.71; 93.99)
Day 22 GMT (95%CI)	140.6 (123.73; 159.73)	158.0 (128.17; 194.73)
GMR (95%CI)	1.68 (1.45; 1.94)	1.69 (1.44; 1.98)
Day 22 SPR (95%CI)	98.00% (94.27; 99.59)	97.56% (91.47; 99.70)
Day 22 SCR (95%CI)	16.67% (11.09; 23.61)	14.63% (7.80; 24.17)

Source 5.3.5.3 table 4b-5b* / 4a-5a**Per protocole analysis
Seropositivity rates: percentage of subjects with HI titers ⩾1:10 ; SPR seroprotection rates: percentage of subjects with HI titers ⩾1:40; 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: GMR Geometric mean ratio GMT D22/D1.

Study V130_12

Title of Study: A Phase III/IV, Stratified, Randomized, Observer Blind, Multicentre Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥2 Years to <18 Years of Age.

Methods

Study Participants

Planned: Approximately 7692 healthy male and female subjects between 2 and <18 years of age were planned to be enrolled, randomized 1:1 between QIVc and the comparator group (receiving a non-influenza licensed Menveo vaccine), over a minimum of 3 influenza seasons. A subset of subjects was required to provide a blood sample and immunogenicity assessments were to be conducted. The subset was to comprise a total of maximum 444 subjects per season in the 2 to <9 years of age cohort for the second and for the third season.

Analysed: A total of 4514 subjects 2 to <18 years of age were enrolled and randomized into the study to receive QIVc or comparator vaccine. Of these, 4513 subjects were exposed to study treatments (2258 received QIVc and 2255 received comparator). In total, 721 subjects 2 to <9 years of age were included in the immunogenicity analyses (364 received QIVc and 357 received comparator).

Subject Characteristics and Main Criteria for Inclusion and Exclusion

Inclusion Criteria

Healthy male and female subjects 2 to <18 years of age on the day of the first study vaccination.

Exclusion Criteria

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

- Clinical signs of fever and/or an oral temperature of ≥100.4°F (38.0°C) within 3 days prior to vaccination.
- Received influenza vaccination or had documented influenza disease in the last 6 months;
- Received prior Meningococcal ACWY vaccination that conflicted with national recommendations or local practices for the timing of the primary or the booster vaccination;
- A known history of any anaphylaxis, serious vaccine reactions or hypersensitivity to any of the vaccine components;
- Medical conditions or treatments contraindicating intramuscular vaccination.
- Any clinical condition that, in the opinion of the investigator, may have interfered with the results of the study or pose additional risk to the subject due to participation in the study.

Treatments

The two treatments consist of one tetravalent QIVc and a non-influenza vaccine (Meningococcal ACWY vaccine, Menveo). The placebo for subjects in both groups, who were not previously vaccinated and received a second vaccination for blinding purposes, was a 0.9% saline for injection, clear, colourless liquid. The dose administered was 0.5 ml. Vaccination was performed intramuscularly, preferably in the deltoid muscle of the non-dominant arm.

The active drug substance consisted of 15 µg of HA of each of the four viral strains recommended by the WHO and Committee for Medicinal Products for Human Use (CHMP) for the 2017 season in the Southern Hemisphere, and seasons 2017/2018 and 2018/2019 in the Northern Hemisphere.

Objectives

Primary Efficacy Objective:

To demonstrate the absolute vaccine efficacy (aVE) of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR or culture-confirmed influenza, due to any influenza Type A and B strain in subjects 2 to <18 years of age. The success criterion used for this primary objective was as follows: The efficacy of the QIVc was demonstrated if the lower limit (LL) of the 2-sided 95% confidence interval (CI) for VE was above 20%.

The co-primary efficacy objective was to be assessed on condition that the primary efficacy objective was successfully demonstrated:

Co-Primary Efficacy Objective: to demonstrate the aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR- or culture- confirmed influenza, due to any influenza Type A and B strain in subjects 3 to <18 years of age.

The success criterion used for this co-primary objective was as follows: The efficacy of the QIVc was demonstrated if the LL of the 2-sided 95% CI for VE was above 30%.

Secondary Efficacy Objectives:

The following objective was evaluated in the age cohorts: 2 to <9 years of age, 4 to <18 years of age, and 9 to <18 years of age:

1. to demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR- or culture-confirmed influenza due to any influenza Type A and B strain.

2. to demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR-confirmed influenza due to any influenza Type A and B strain.

3. to demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of culture-confirmed influenza due to any influenza Type A and B strain.

4. to demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of culture-confirmed influenza caused by influenza strains antigenically matched to the strains selected for the seasonal vaccine.

Secondary Immunogenicity Objective:

To characterize the immunogenicity of QIVc by hemagglutination inhibition (HI) assay 3 weeks after the last vaccination in a subset of subjects in the age cohort 2 to <9 years of age.

Exploratory Efficacy Objective:

The following objectives were evaluated in the age cohorts: 2 to <18 years of age:

1. to further characterize the efficacy of QIVc, with specific attention for all-cause mortality, all-cause pneumonia, and all-cause otitis media.

2. to describe the aVE of QIVc versus a non-influenza comparator determined by the occurrence of culture-confirmed illness caused by influenza H3N2 virus strains antigenically matched to the influenza H3N2 A/Singapore/GP2050/2015 (cell seed) strain.

Exploratory Immunogenicity Objective:

To further characterize the immune response in a subset of subjects in the age cohort 2 to <9 years of age, using other assays, such as microneutralization (MN).

Endpoints

Efficacy:

Primary Efficacy Endpoints:

The primary and co-primary efficacy endpoints were defined as the time from the last study vaccination to the onset of the first occurrence of either RT-PCR or culture-confirmed influenza (time-to-event analyses) due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.
An ILI case was defined as body temperature of ≥100.0°F/ ≥37.8°C (ie, fever) along with any of the following symptoms: cough, sore throat, nasal congestion, or rhinorrhoea. An influenza case was defined as RT-PCR confirmed or culture-confirmed influenza in a subject who met the mentioned criteria for ILI.

Secondary Efficacy Endpoints:

- For secondary objective 1: the time from the last study vaccination to the onset of the first occurrence of either RT-PCR or culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.
- For secondary objective 2: the time from the last study vaccination to the onset of the first occurrence of RT- PCR confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.
- For secondary objective 3: the time from the last study vaccination to the onset of the first occurrence of culture- confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.
- For secondary objective 4: the time from the last study vaccination to the onset of the first occurrence of culture- confirmed influenza due to influenza Type A or B strain antigenically matched to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.

Exploratory Efficacy Endpoints:

•For exploratory efficacy objective 1:

- number of deaths as derived from serious adverse event (SAE) forms
- number of subjects with pneumonia as derived from AE forms
- number of subjects with physician-confirmed otitis media as derived from AE forms

• For exploratory efficacy objective 2: the time from the last study vaccination to the onset of the first occurrence of culture-confirmed influenza, due to any influenza H3N2 virus strains antigenically matched to the influenza H3N2 A/Singapore/GP2050/2015 (cell seed) strain, occurring at >14 days after the last vaccination and until the end of the influenza season.

Immunogenicity:

Secondary Immunogenicity Endpoints:

The immunogenicity of study vaccine was assessed 21 days after the last vaccine administration by measuring the HI assay to the 4 viral strains included in the vaccine. The measures for assessing immunogenicity as determined by HI were as follows:

- HI Geometric mean titres (GMTs) on Day 1 (all subjects), Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.
- Percentage of subjects achieving seroconversion (defined as: either a prevaccination HI titre <1:10 and a postvaccination HI titre ≥1:40 or a prevaccination HI titre ≥1:10 and a ≥4 fold increase in postvaccination HI titre) on Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.
- HI Geometric mean ratio (GMR): of Day 22/Day 1 (all "previously vaccinated" subjects receiving a single vaccine dose) or Day 29/Day 1 and Day 50/Day 1 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.
- Percentage of subjects with HI titre ≥1:40 on Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.

Exploratory Immunogenicity Endpoint:

In the event of additional immunogenicity analyses, such as MN, the immune response was characterized in a similar manner as described in the secondary immunogenicity endpoints.

Sample size

This study was planned using a group sequential design, with one or more interim analyses for efficacy using O'Brien-Fleming efficacy bounds. The statistical test performed depended only on the number of confirmed ILI cases (events), so the sample size estimate was only for operational reasons (an estimate of number of subjects needed to assess the endpoint).

Primary Efficacy Objective ≥2 years to <18 years of age

Estimated sample size to arrive at 298 events, is 4,814 evaluable subjects (or 2,407 evaluable subjects per treatment group), assuming attack rate in non-influenza comparator vaccine subjects of 8%, vaccine efficacy of 45%, and the risk of infection contained entirely within period covered by follow-up. Accounting for early dropout and uncertainty about the assumed parameters, 5,349 subjects are planned to be enrolled to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 20% for the primary endpoint assessment, with approximately 90% power.

Co-primary Efficacy Objective ≥3 years to <18 years of age

Assuming a true vaccine efficacy of 50% it was calculated that approximately 381 observed confirmed ILI cases would be needed to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30% with approximately 90% power. The statistical test performed will depend only on number of confirmed ILI cases (events), so sample size estimate is only for operational reasons. Estimated sample size to arrive at 381 events, is 6,350 evaluable subjects (or 3,175 evaluable subjects per treatment group), assuming attack rate in non-influenza comparator vaccine subjects of 8%, assumed vaccine efficacy of 50%, VE is greater than 30%, and the risk of infection contained entirely within period covered by follow-up. Accounting for early dropout and uncertainty about the assumed parameters, 7,056 subjects are planned to be enrolled to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30%.

Table below summarizes the power calculations assumptions and the number of events required to meet primary and co-primary endpoint.

Table 23. Power calculation for Primary and Co-Primary Endpoints

Age group	VE Success Criteria	Assumed Vaccine Efficacy	Influenza attack rate in comparator group	Power	Minimal total evaluable subjects per Treatment Group	Minimal enrolled subjects needed per Treatment group*	Minimal total Number Enrolled*	Total Number of ILIs to demonstrate LL 95% CI for VE is > 30% or 20%
≥2 years to <18 years of age	20%	45%	8%	>90%	2,407	2,674	5,349	298
≥3 years to <18 years of age	30%	50%	8%	>90%	3,175	3,528	7,056	381

*accounted for early dropout and uncertainty

Randomisation

A total of 4514 subjects 2 to <18 years of age were enrolled and randomized in a 1:1 ratio to QIVc or non-influenza comparator vaccine, Menveo® (GSK Biologicals S.A.), a Neisseria meningitidis serogroup A, C, W-135, Y conjugate vaccine. The randomization was stratified by age (2 to < 9 years and 9 to < 18 years). Subjects between 2 to < 9 years of age were further stratified by previous influenza vaccine status. Study subjects were scheduled to receive either a single dose of 0.5 mL of the study vaccine or a two dose study vaccination regimen separated by approximately 4 weeks as clinically indicated

depending on age and previous influenza vaccination history according to paediatric influenza vaccine dosing recommendations (Grohskopf et al., 2015) and consistent with international guidelines.

Blinding

This trial was designed as an observer blind study.

Statistical methods

Analysis Sets:

• Full Analysis Set (FAS) Efficacy: All subjects in the All-Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.

• FAS Immunogenicity: All subjects in the All-Enrolled Set, immunogenicity subset who received at least one dose of study vaccine and provided evaluable serum samples at both baseline and after the last vaccination.

• Per Protocol Set (PPS) Efficacy/Immunogenicity Set: All subjects in the FAS Efficacy / Immunogenicity who:

- Correctly received the vaccine (i.e., received the vaccine to which the subject was randomized and at the scheduled time point[s]).
- Had no protocol deviations leading to exclusion as defined prior to unblinding / or analysis.
- Were not excluded due to other reasons (e.g., subjects who withdrew informed consent) as defined prior to unblinding or analysis.

• Solicited Safety Set (Solicited Local and Systemic Adverse Events and Other Solicited Adverse Events): All subjects in the Exposed Set who had gone through any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics.

Unsolicited Safety Set (Unsolicited Adverse Events): All subjects in the Exposed Set who had gone through any AE assessments, i.e., a subject did not have to have any AEs to be included in this population.

• Overall Safety Set: All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

Analysis of Efficacy:

(Co-)primary VE analyses were based on the Efficacy FAS and repeated on the Efficacy PPS.

The primary measure of efficacy was the estimate of aVE of QIVc relative to the non-influenza comparator vaccine for preventing first-occurrence influenza-confirmed disease by either RT-PCR-confirmed or culture-confirmed influenza strains contained in QIVc and the non-influenza comparator, regardless of antigenic match.

A time-to-event methodology based on a proportional hazard model was used for all efficacy analyses. aVE against first or only confirmed influenza cases was determined using a standard formula: aVE = 1 - HR where HR is the hazard ratio for influenza confirmed (either RT-PCR-confirmed or culture-confirmed) ILI in the QIVc group versus the non-influenza comparator group. The HR was estimated by a proportional hazards regression model for which the following null (H0) and alternative (H1) hypotheses were tested:

H0: $1 - HR \leq 0.2$ versus H1: $1 - HR > 0.2$

where HR is a hazard ratio of QIVc versus non-influenza comparator and VE is vaccine efficacy. The primary objective was achieved if the LL of the 2-sided CI of the VE estimate, with at least 95% coverage in a multiple sequential hypothesis testing, exceeded 0.2 in subjects 2 to <18 years of age.

The co-primary objective was achieved if the LL of the 2-sided CI of the VE estimate, with at least 95% coverage in a multiple sequential hypothesis testing, exceeded 0.3 in subjects 3 to <18 years of age.

The model used to estimate aVE for the secondary efficacy objectives was similar to the model used for the primary efficacy objectives.

Immunogenicity:

Immunogenicity analyses were based on the Immunogenicity FAS and repeated on the Immunogenicity PPS.

All statistical analyses for HI titres were performed on the logarithmically (base 10) transformed values. Individual HI titres below the detection limit (<10) were set to half of that limit (5).

Both adjusted and unadjusted estimates for GMTs, GMRs and pertaining 2-sided 95% CIs were calculated assuming log-normal distribution of the titres and were completed by providing minimum, maximum and median titres for each vaccine group.

Binary data (i.e., percentages of subjects with seroconversion and with titre ≥1:40) were summarized for each group and were reported together with 2-sided 95% CIs calculated according to Clopper and Pearson (1934). No multiplicity adjustment to the CI levels were implemented.

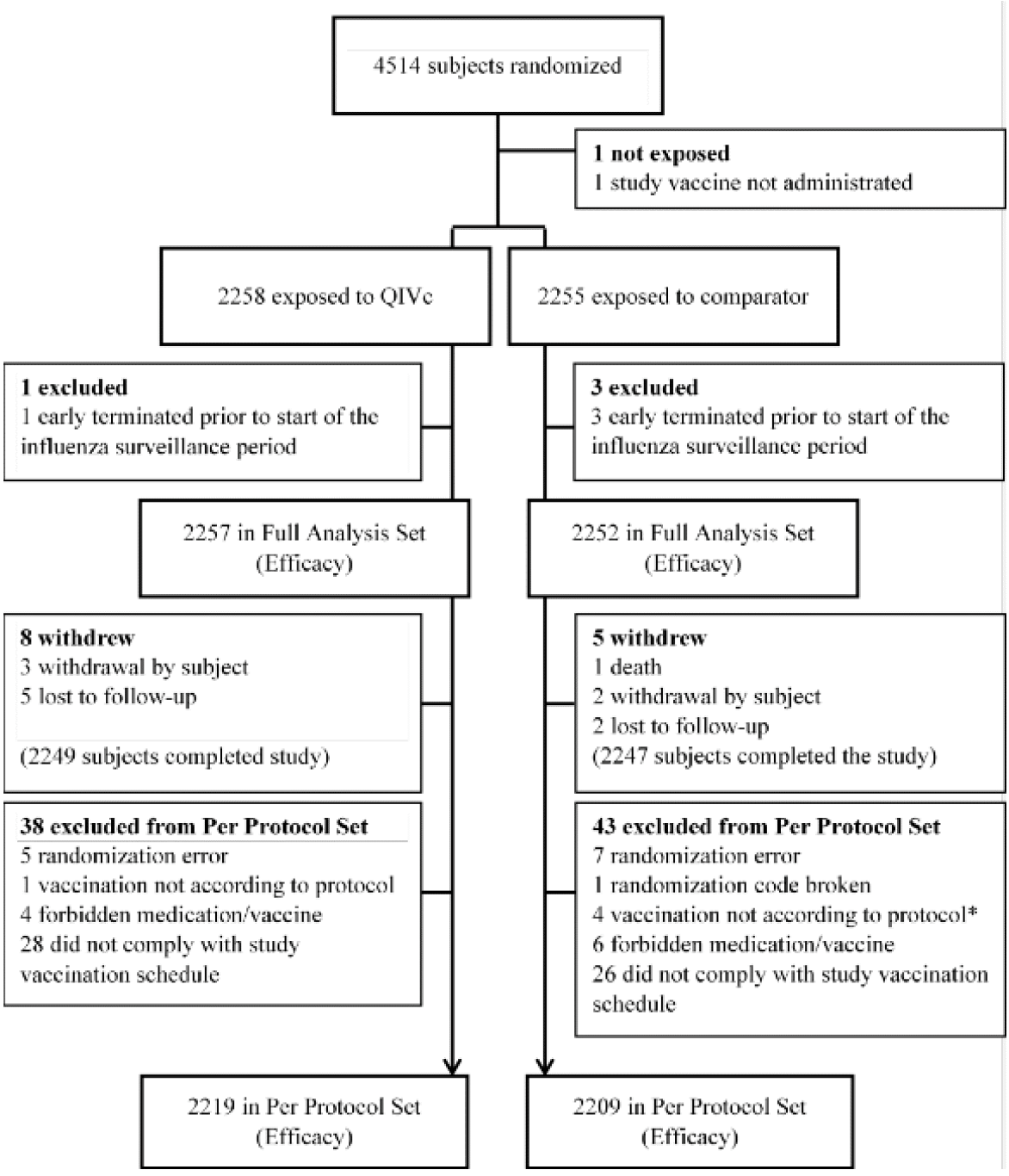
For immunogenicity data, it was reasonable to consider missing immunogenicity values as missing completely at random, i.e., not informative. Therefore, the key secondary analysis was a complete case analysis only, without introducing any bias. Imputation methods were not used.

Results

Participant flow

A total of 4514 subjects were enrolled in Study V130_12. The population used for the efficacy analysis was the Efficacy Full Analysis Set (FAS) which included all enrolled subjects that were randomized, received at least one study vaccination and provided efficacy data. Five enrolled subjects were excluded from the Efficacy, FAS population. Efficacy analyses were repeated with the Efficacy Per Protocol Set (PPS) which included all FAS subjects that correctly received the vaccines, had no protocol deviations leading to exclusion and were not excluded due to other reasons defined prior to unblinding or analysis. In total, 9 (0.4%) subjects in the QIVc group and 9 (0.4%) subjects in the comparator group were withdrawn from the study. The number of enrolled subjects and disposition by age cohort and study treatment are shown in Figure 3.

Figure 3. Study V130_12 subject allocation flowchart



Recruitment

Study V130_12 was conducted over 3 seasons, starting in SH 2017 (25 May 2017), followed by NH 2017-2018 and NH 2018-2019 (30 Sep 2019). Subjects were recruited in 8 countries over these 3 seasons, Australia, Philippines and Thailand in the first season, Estonia and Finland in the second season and Estonia, Finland, Lithuania, Poland and Spain in the third season.

Conduct of the study

A total of 4514 subjects were enrolled in Study V130_12. The population used for the efficacy analysis was the Efficacy Full Analysis Set (FAS) which included all enrolled subjects that were randomized, received at least one study vaccination and provided efficacy data. Five enrolled subjects were excluded from the_Efficacy, FAS population. Efficacy analyses were repeated with the Efficacy Per Protocol Set (PPS) which included all FAS subjects that correctly received the vaccines, had no protocol deviations leading to exclusion and were not excluded due to other reasons defined prior to unblinding or analysis. In total, 9 (0.4%) subjects in the QIVc group and 9 (0.4%) subjects in the comparator group were withdrawn from the study, the reasons for discontinuation are summarized in Section 2.7.3, In total, 9 (0.4%) subjects in the QIVc group and 9 (0.4%) subjects in the comparator group were withdrawn from the study, the reasons for discontinuation are summarized in Table 24.

Table 24 Summary of Study Terminations in Subjects 2 to < 18 years of Age – All Enrolled, Study V130_12

	QIVc N=2258 n (%)	**Comparator N=2256 n (%)**	**Total N=4514 n (%)**
Total number of subjects enrolled	2258 (100.0)	2256 (100.0)	4514 (100.0)
Total number of subjects exposed	2258 (100.0)	2255 (99.96)	4513 (99.98)
Completed protocol	2249 (99.60)	2247 (99.60)	4496 (99.60)
Primary Reason for discontinuation from the study:	**9 (0.4)**	**9 (0.4)**	**18 (0.4)**
Adverse event	0	0	0
Death	0	1 (0.04)	1 (0.02)
Withdrawal by subject	3 (0.13)	3 (0.13)	6 (0.13)
Lost to follow-up	5 (0.22)	2 (0.09)	7 (0.16)
Administrative reason	0	0	0
Protocol violation	0	0	0
Other	1 (<1)	3 (0.13)	4 (0.09)

Source: Section 5.3.5.1, CSR V130_12 Table 10-1
Abbreviations: QIVc = cell-derived quadrivalent subunit influenza virus vaccine.
Note 1: The non-influenza comparator is meningococcal (Serogroup ACWY) conjugate vaccine.
Note 2: Enrolled subjects were all screened subjects who signed informed consent and provided demographic and/or other baseline screening measurements, regardless of the subject's randomization and vaccination status in the study, and received a Subject ID.
Note 3: Exposed subjects were All Enrolled subjects who receive a study treatment. One subject refused any study vaccine, was not vaccinated and discontinued the study.
Note 4: Percentages are based on the number of subjects in each vaccine group.

Demographic and Baseline data

Overall, 2395 subjects (53.1%) were enrolled in Southern Hemisphere countries and 2119 (46.9%) in Northern Hemisphere countries. The majority of subjects were enrolled in Season 1 (n=2395; 53.1%) with most subjects from the Philippines (n=1800). In Season 2, 919 subjects (20.4%) were enrolled in Estonia and Finland and 1200 (26.6%) in Season 3. Both in Season 2 and 3 the majority of subjects were enrolled in Estonia (Season 2: n=600; Season 3: n=598).

The population was well balanced between the sexes (48.5% female and 51.5% male). All subjects were between 2 and 18 years of age in agreement with the intended study population. The overall mean (SD) age was 8.8 (4.1) years. Approximately half of the study population (50.7%) was between 2 to <9 years of age. The youngest age category (between 2 to <4 years of age) comprised 9.6% of the study population.

Overall, the majority (65.9%) of subjects (n=4514) were previously vaccinated against influenza. Of the subjects 2 to <9 years of age (n=2289), 32.8% were previously vaccinated against influenza. All of the subjects 9 to <18 years of age (100%) were categorized as previously vaccinated against influenza as age (9 to <18 years of age) was used as stratify these subjects to receive 1 dose of study vaccine. There was no notable difference in the distribution of demographic and baseline characteristics (age, sex, race, ethnic origin or country of enrolment) between the 2 vaccine groups in the All-Enrolled Set, nor was any difference between the 2 to <18 (n=4514) and 3 to <18 years of age (n=4414) cohorts.

Table 25 Demographics and Baseline Characteristics – All Enrolled Set

	QIVc N=2258	Comparator N=2256	Total N=4514
Age (years)			
n	2258	2256	4514
Mean (SD)	8.7 (4.0)	8.9 (4.1)	8.8 (4.1)
Age Group (n[%])			
2 to < 18 years	2258 (100.0)	2256 (100.0)	4514 (100.0)
3 to < 18 years	2209 (97.8)	2205 (97.7)	4414 (97.8)
4 to < 18 years	2046 (90.6)	2036 (90.2)	4082 (90.4)
9 to < 18 years	1112 (49.2)	1113 (49.3)	2225 (49.3)
2 to <4 years	212 (9.4)	220 (9.8)	432 (9.6)
2 to < 9 years	1146 (50.8)	1143 (50.7)	2289 (50.7)
Sex (n[%])			
N	2258	2256	4514
Male	1152 (51.0)	1174 (52.0)	2326 (51.5)
Female	1106 (49.0)	1082 (48.0)	2188 (48.5)
Race (n[%])			
N	2258	2256	4514
American Indian or Alaska Native	0	0	0
Asian	1106 (49.0)	1100 (48.8)	2206 (48.9)
Black or African American	1 (<0.1)	0	1 (<0.1)
Native Hawaiian or Other Pacific Islander	0	2 (0.1)	2 (<0.1)
White	1140 (50.5)	1139 (50.5)	2279 (50.5)
Other	11 (0.5)	15 (0.7)	26 (0.6)
Ethnic Origin (n[%])			
n	2258	2256	4514
Hispanic or Latino	11 (0.5)	11 (0.5)	22 (0.5)
Not Hispanic or Latino	2245 (99.4)	2245 (99.5)	4490 (99.5)
Not Reported	2 (0.1)	0	2 (<0.1)
Unknown	0	0	0
Country (n[%])			
n	2258	2256	4514
Australia	96 (4.3)	99 (4.4)	195 (4.3)
Estonia	599 (26.5)	599 (26.6)	1198 (26.5)
Finland	168 (7.4)	158 (7.0)	326 (7.2)
Lithuania	142 (6.3)	150 (6.6)	292 (6.5)
Philippines	902 (39.9)	898 (39.8)	1800 (39.9)
Poland	147 (6.5)	151 (6.7)	298 (6.6)
Spain	3 (0.1)	2 (0.1)	5 (0.1)
Thailand	201 (8.9)	199 (8.8)	400 (8.9)
Previous Influenza Vaccination (n[%])			
n	2258	2256	4514
Previously vaccinated	1488 (65.9)	1487 (65.9)	2975 (65.9)
Not previously vaccinated	770 (34.1)	769 (34.1)	1539 (34.1)
Season (n[%])			
n	2258	2256	4514

	QIVc N=2258	Comparator N=2256	Total N=4514
Season 1	1199 (53.1)	1196 (53.0)	2395 (53.1)
Season 2	459 (20.3)	460 (20.4)	919 (20.4)
Season 3	600 (26.6)	600 (26.6)	1200 (26.6)
Body Mass Index (kg/m^2)			
n	2258	2255	4513
Mean (SD)	17.5 (3.7)	17.6 (3.8)	17.6 (3.7)
Median	16.5	16.5	16.5

Source: Section 5.3.5.1, CSR V130_12 Table 10-6
Abbreviations: QIVc = cell-derived quadrivalent subunit influenza virus vaccine; SD = standard deviation.
Note: The non-influenza comparator was meningococcal (Serogroup ACWY) conjugate vaccine.

Numbers analysed

Efficacy Population, Study V130_12

A total of 4514 subjects were enrolled in Study V130_12. The population used for the efficacy analysis was the Efficacy Full Analysis Set (FAS) which included all enrolled subjects that were randomized, received at least one study vaccination and provided efficacy data. Five enrolled subjects were excluded from the Efficacy, FAS population. Efficacy analyses were repeated with the Efficacy Per Protocol Set (PPS) which included all FAS subjects that correctly received the vaccines, had no protocol deviations leading to exclusion and were not excluded due to other reasons defined prior to unblinding or analysis.

Immunogenicity Population, Study V130_12

The population used for the immunogenicity analysis based on the HI and MN assay was the FAS Immunogenicity. This population was defined as all enrolled subjects aged 2 to < 9 years that were randomized, received at least one study vaccination and provided HI assay immunogenicity data at baseline and after last vaccination. The PPS immunogenicity population was the same as the FAS but excluded subjects with protocol deviations leading to exclusion or due to other reasons defined prior to unblinding or analysis.

The subject populations are presented in the following table:

Table 26. Overview of efficacy and Immunogenicity Sets analysed-as randomised

	QIVc N=2258 n (%)	Comparator N=2256 n (%)	Total N=4514 n (%)
All Enrolled Set	2258 (100.0)	2256 (100.0)	4514 (100.0)
All Exposed Set	2258 (100.0)	2255 (99.96)	4513 (99.98)
FAS, Efficacy, 2 to <18 yrs	2257 (99.96)	2252 (99.82)	4509 (99.89)
PPS, Efficacy, 2 to <18 yrs	2219 (98.27)	2209 (97.92)	4428 (98.09)
FAS, Immunogenicity, 2 to <9 yrs	364 (16.12)	357 (15.82)	721 (15.97)
PPS, Immunogenicity, 2 to <9 yrs	349 (15.46)	339 (15.03)	688 (15.24)

Source: Table 14.1.1.1 and Table 14.1.1.1.1.

Abbreviations: FAS = full analysis set; HI = hemagglutination inhibition; MN = microneutralization; PPS = per protocol set; QIVc = cell-derived quadrivalent subunit influenza virus vaccine; yrs = years

Note 1: The non-influenza comparator was meningococcal (Serogroup ACWY) conjugate vaccine.

Note 2: As Randomized: according to the vaccine a subject was designated to receive, which may have been different from the vaccine the subject actually received.

Note 3: Only in Season 2 and 3 a subset of subjects 2 to <9 years of age were enrolled into the immunogenicity subset.

Outcomes and estimation

EFFICACY

PRIMARY OBJECTIVE: The primary objective was to demonstrate the absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR or culture-confirmed influenza due to any influenza Type A and B strain in subjects 2 to < 18 years of age.

The primary efficacy objective was successfully demonstrated; therefore, the co-primary efficacy objective was assessed. This objective was to demonstrate the absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR- or culture-confirmed influenza, due to any influenza Type A and B strain in subjects 3 to < 18 years of age. The co-primary endpoint was tested sequentially without adjustment of Type I error for the population.

The primary and co-primary efficacy endpoints were defined as the time from the last study vaccination to the onset of the first occurrence of RT-PCR- or culture-confirmed influenza, due to any influenza Type A or B strain, and regardless of an antigenic match to the strains selected for the seasonal vaccine that occurred more than 14 days after the last vaccination until the end of the influenza season. The primary and co-primary endpoints were met if the lower limit of the 2-sided 95% CI of the absolute vaccine efficacy estimate was greater than 20% (primary endpoint) or greater than 30% (co-primary endpoint) using the protocol definition of ILI for the entire age range. The primary and co-primary were assessed in the FAS Efficacy.

In the FAS Efficacy, for 539 of the 4509 subjects 2 to < 18 years of age RT-PCR- or culture-confirmed influenza caused by any Type A or Type B strain were observed, i.e., in 175 subjects in the QIVc group (7.8%) and 364 subjects in the comparator group (16.2%) (Table 27).

The analysis shows that QIVc prevented RT-PCR or culture confirmed influenza caused by any Type A or B strain in subjects 2 to < 18 years of age (primary efficacy endpoint) and 3 to < 18 years of age (co-primary endpoint). The VE of QIVc in children 2 to < 18 years of age was 54.6% (95% CI: 45.7 to 62.1). The success criterion was met as the LL of the 2-sided 95% CI was above 20%. The VE of QIVc in children 3 to < 18 years of age was 54.0% (95% CI: 44.8 to 61.7). The success criterion was met as the LL of 95% CI for VE is above 30% (Table 27 below).

Table 27 Number of subjects with first-occurrence RT-PCR-Confirmed or Culture confirmed influenza and absolute vaccine efficacy (95% CI), overall in subjects 2 to < 18 years of age and 3 to <18 years of age-FAS Efficacy

Any Strain	QIVc (n[%])	Comparator (n[%])	aVE[c] (95% CI)	Success Criteria Met (Yes/No)
2 to < 18 Years of Age[a]	N = 2257	N = 2252		
RT-PCR or Culture Confirmed, Number of cases (attack rate)	175 (7.8)	364 (16.2)	54.63 (45.67, 62.12)	Yes
3 to < 18 Years of Age[b]	N = 2208	N = 2201		
RT-PCR or Culture Confirmed, Number of cases (attack rate)	171 (7.7)	351 (15.9)	54.03 (44.80, 61.71)	Yes

SECONDARY OBJECTIVES were intended to demonstrate the absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by the first occurrence of either RT- PCR- and/or culture-confirmed influenza due to any Type A and B strain, and culture- confirmed antigenically matched to the vaccine strains. These endpoints were evaluated in different age cohorts of 2 to <4, 4 to < 18, 2 to < 9, and 9 to < 18 years of age.

Subjects 2 to <4 years of age: In subjects 2 to <4 years of age, the overall VE of QIVc against RT-PCR- or culture- confirmed influenza was **62.66% (95% CI: 38.06; 77.49).**

Subjects 4 to <18 years of age: In subjects 4 to <18 years of age, the overall VE of QIVc against any RT-PCR- or culture- confirmed influenza was **53.33% (95% CI: 43.38; 61.54).** For further details see Table below.

Table 28 Number of subjects with First-occurrence RT-PCR-confirmed or culture confirmed influenza and absolute vaccine efficacy (95% CI), Overall and by Strain, in Subjects 2 to <4 years of age and 4 to <18 years of age-FAS Efficacy

	2 to <4 Years of Age			4 to <18 Years of Age		
	QIVc N=212 n (%)	Comparator N=220 n (%)	aVE[a] (95% CI)	QIVc N=2045 n (%)	Comparator N=2032 n (%)	aVE[a] (95% CI)
RT-PCR or Culture Confirmed						
Any Strain - Number of cases (attack rate)	**21 (9.9)**	**54 (24.5)**	**62.66 (38.06, 77.49)**	**154 (7.5)**	**310 (15.3)**	**53.33 (43.38, 61.54)**
Type A	13 (6.1)	35 (15.9)	63.69 (31.21, 80.83)	83 (4.1)	179 (8.8)	55.67 (42.47, 65.84)
A/H1N1	3 (1.4)	19 (8.6)	85.79 (51.76, 95.81)	18 (0.9)	86 (4.2)	79.95 (66.66, 87.95)
A/H3N2	8 (3.8)	16 (7.3)	48.71 (-20.73, 78.21)	52 (2.5)	86 (4.2)	40.50 (16.03, 57.83)
Type B	8 (3.8)	19 (8.6)	57.79 (3.16, 81.60)	73 (3.6)	131 (6.4)	46.79 (29.13, 60.05)
RT-PCR Confirmed						
Any Strain - Number of cases (attack rate)	**21 (9.9)**	**54 (24.5)**	**62.66 (38.06, 77.49)**	**154 (7.5)**	**310 (15.3)**	**53.33 (43.38, 61.54)**
Type A	13 (6.1)	35 (15.9)	63.69 (31.21, 80.83)	83 (4.1)	179 (8.8)	55.67 (42.47, 65.84)
A/H1N1	3 (1.4)	18 (8.2)	85.21 (49.57, 95.66)	16 (0.8)	85 (4.2)	81.98 (69.24, 89.45)
A/H3N2	8 (3.8)	15 (6.8)	45.67 (-29.22, 77.16)	51 (2.5)	85 (4.2)	40.92 (16.39, 58.25)
Type B	8 (3.8)	19 (8.6)	57.79 (3.16, 81.60)	73 (3.6)	131 (6.4)	46.79 (29.13, 60.05)
Culture Confirmed						
Any Strain - Number of cases (attack rate)	**14 (6.6)**	**42 (19.1)**	**67.72 (40.76, 82.41)**	**101 (4.9)**	**237 (11.7)**	**59.66 (49.08, 68.05)**
A/H1N1	3 (1.4)	17 (7.7)	84.07 (45.39, 95.35)	14 (0.7)	76 (3.7)	82.27 (68.62, 89.98)
A/H3N2	6 (2.8)	14 (6.4)	56.10 (-15.11, 83.26)	37 (1.8)	61 (3.0)	40.02 (9.74, 60.14)
Type B	5 (2.4)	12 (5.5)	57.74 (-20.33, 85.16)	51 (2.5)	100 (4.9)	50.76 (30.99, 64.86)
Culture Confirmed						
Matched Strain - Number of cases (attack rate)	**9 (4.2)**	**36 (16.4)**	**77.08 (52.27, 89.00)**	**81 (4.0)**	**200 (9.8)**	**61.58 (50.25, 70.33)**

	2 to <4 Years of Age			4 to <18 Years of Age		
	QIVc N=212 n (%)	Comparator N=220 n (%)	aVE[a] (95% CI)	QIVc N=2045 n (%)	Comparator N=2032 n (%)	aVE[a] (95% CI)
A/H1N1	3 (1.4)	17 (7.7)	84.07 (45.39, 95.35)	14 (0.7)	75 (3.7)	82.08 (68.27, 89.88)
A/H3N2	2 (0.9)	9 (4.1)	80.73 (9.75, 95.89)	18 (0.9)	27 (1.3)	33.29 (-21.20, 63.28)
B/Yamagata	4 (1.9)	11 (5.0)	63.73 (-14.24, 88.48)	48 (2.3)	94 (4.6)	50.72 (30.21, 65.20)
B/Victoria	0 (0)	0 (0)	NA (NA, NA)	2 (0.1)	4 (0.2)	NA (NA, NA)
Culture Confirmed						
Unmatched Strain - Number of cases (attack rate)	**5 (2.4)**	**6 (2.7)**	**-5.14 (-247.52, 68.19)**	**20 (1.0)**	**37 (1.8)**	**46.73 (8.21, 69.09)**
A/H1N1	0 (0)	0 (0)	NA (NA, NA)	0 (0)	1 (0.0)	NA (NA, NA)
A/H3N2	4 (1.9)	5 (2.3)	NA (NA, NA)	19 (0.9)	34 (1.7)	45.09 (3.71, 68.68)
Type B	1 (0.5)	1 (0.5)	NA (NA, NA)	1 (0.0)	2 (0.1)	NA (NA, NA)

Source: Table 14.2.0.1.1.3, Table 14.2.0.1.1.4, Table 14.2.0.2.1.3, Table 14.2.0.2.1.4, Table 14.2.0.3.1.3, Table 14.2.0.3.1.4, Table 14.2.0.4.1.3, Table 14.2.0.4.1.4, Table 14.2.0.4.5.3, and Table 14.2.0.4.5.4.

Abbreviations: aVE = absolute vaccine efficacy; CI = confidence interval; men ACWY = meningococcal (Serogroup ACYW-135) conjugate vaccine; QIVc = cell-derived quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription polymerase chain reaction.

[a] Adjusted aVE is presented.

Note: The non-influenza comparator is meningococcal (Serogroup ACYW-135) conjugate vaccine. Previously vaccinated subjects under 9 years of age and all subjects 9 years of age and older received 1 vaccination (QIVc or men ACWY) on Day 1. For subjects under 9 years of ages who had not been previously vaccinated, 2 vaccinations were administered; the comparator vaccine group received men ACWY on Day 1 followed by a saline placebo vaccine on Day 29, whereas the QIVc group received 2 QIVc vaccinations on Days 1 and 29.

Subjects 2 to <9 years of age: In subjects 2 to <9 years of age, the overall VE of QIVc against any RT-PCR- or culture- confirmed influenza was 50.51% (95% CI: 38.43; 60.22). These results are detailed in the following Table 29.

Subjects 9 to <18 years of age: In subjects 9 to <18 years of age, the overall VE of QIVc against any RT-PCR- or culture-confirmed influenza was 61.85% (95% CI: 47.37; 72.34). See results in the following Table 29.

Table 29. Number of Subjects with First-occurrence RT-PCR-confirmed or culture confirmed influenza and absolute vaccine efficacy (95% CI), Overall and by Strain, in Subjects 2 to <9 years of age and 9 to <18 years of age-FAS Efficacy

	2 to <9 Years of Age			9 to <18 Years of Age		
	QIVc N=1146 n (%)	Comparator N=1142 n (%)	aVE[a] (95% CI)	QIVc N= 1111 n (%)	Comparator N= 1110 n (%)	aVE[a] (95% CI)
RT-PCR or Culture Confirmed						
Any Strain - Number of cases (attack rate)	**123 (10.7)**	**234 (20.5)**	**50.51 (38.43, 60.22)**	**52 (4.7)**	**130 (11.7)**	**61.85 (47.37, 72.34)**
Type A	68 (5.9)	141 (12.3)	54.12 (38.72, 65.65)	28 (2.5)	73 (6.6)	62.58 (42.15, 75.80)
A/H1N1	17 (1.5)	81 (7.1)	79.95 (66.17, 88.12)	4 (0.4)	24 (2.2)	83.46 (52.31, 94.26)
A/H3N2	39 (3.4)	57 (5.0)	32.82 (-0.96, 55.30)	21 (1.9)	45 (4.1)	53.93 (22.66, 72.55)
Type B	57 (5.0)	93 (8.1)	40.29 (16.96, 57.06)	24 (2.2)	57 (5.1)	59.37 (34.54, 74.79)
RT-PCR Confirmed						
Any Strain - Number of cases (attack rate)	**123 (10.7)**	**234 (20.5)**	**50.51 (38.43, 60.22)**	**52 (4.7)**	**130 (11.7)**	**61.85 (47.37, 72.34)**
Type A	68 (5.9)	141 (12.3)	54.12 (38.72, 65.65)	28 (2.5)	73 (6.6)	62.58 (42.15, 75.80)
A/H1N1	16 (1.4)	80 (7.0)	80.87 (67.26, 88.82)	3 (0.3)	23 (2.1)	87.04 (56.84, 96.11)
A/H3N2	39 (3.4)	55 (4.8)	30.28 (-5.09, 53.75)	20 (1.8)	45 (4.1)	56.13 (25.72, 74.09)
Type B	57 (5.0)	93 (8.1)	40.29 (16.96, 57.06)	24 (2.2)	57 (5.1)	59.37 (34.54, 74.79)
Culture Confirmed						
Any Strain - Number of cases (attack rate)	**79 (6.9)**	**190 (16.6)**	**60.78 (49.01, 69.83)**	**36 (3.2)**	**89 (8.0)**	**60.72 (42.14, 73.33)**
A/H1N1	13 (1.1)	73 (6.4)	82.86 (69.06, 90.50)	4 (0.4)	20 (1.8)	80.05 (41.64, 93.18)
A/H3N2	28 (2.4)	48 (4.2)	42.82 (8.86, 64.12)	15 (1.4)	27 (2.4)	44.78 (-3.81, 70.62)
Type B	38 (3.3)	70 (6.1)	46.73 (20.93, 64.12)	18 (1.6)	42 (3.8)	58.42 (27.77, 76.07)
Culture Confirmed						
Matched Strain - Number of cases (attack rate)	**64 (5.6)**	**164 (14.4)**	**63.04 (50.66, 72.32)**	**26 (2.3)**	**72 (6.5)**	**64.78 (44.84, 77.51)**

	2 to <9 Years of Age			9 to <18 Years of Age		
	QIVc N=1146 n (%)	Comparator N=1142 n (%)	aVE[a] (95% CI)	QIVc N= 1111 n (%)	Comparator N= 1110 n (%)	aVE[a] (95% CI)
A/H1N1	13 (1.1)	72 (6.3)	82.63 (68.63, 90.38)	4 (0.4)	20 (1.8)	80.05 (41.64, 93.18)
A/H3N2	14 (1.2)	25 (2.2)	45.81 (-4.26, 71.84)	6 (0.5)	11 (1.0)	44.76 (-49.43, 79.58)
B/Yamagata	36 (3.1)	68 (6.0)	48.08 (22.23, 65.34)	16 (1.4)	37 (3.3)	57.89 (24.29, 76.58)
B/Victoria	1 (0.1)	0 (0)	NA (NA, NA)	1 (0.1)	4 (0.4)	NA (NA, NA)
Culture Confirmed						
Unmatched Strain - Number of cases (attack rate)	**15 (1.3)**	**26 (2.3)**	**42.86 (-7.89, 69.74)**	**10 (0.9)**	**17 (1.5)**	**41.75 (-27.21, 73.33)**
A/H1N1	0 (0)	1 (0.1)	NA (NA, NA)	0 (0)	0 (0)	NA (NA, NA)
A/H3N2	14 (1.2)	23 (2.0)	39.78 (-17.03, 69.02)	9 (0.8)	16 (1.4)	44.26 (-26.14, 75.37)
Type B	1 (0.1)	2 (0.2)	NA (NA, NA)	1 (0.1)	1 (0.1)	NA (NA, NA)

Source: Table 14.2.0.1.1.5, Table 14.2.0.1.1.6, Table 14.2.0.2.1.5, Table 14.2.0.2.1.6, Table 14.2.0.3.1.5, Table 14.2.0.3.1.6, Table 14.2.0.4.1.5, Table 14.2.0.4.1.6, Table 14.2.0.4.5.5, and Table 4.2.0.4.5.6.

Abbreviations: aVE = absolute vaccine efficacy; CI = confidence interval; men ACWY = meningococcal (Serogroup ACYW-135) conjugate vaccine; QIVc = cell-derived quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription polymerase chain reaction.

[a] Adjusted aVE is presented.

Note: The non-influenza comparator is meningococcal (Serogroup ACYW-135) conjugate vaccine. Previously vaccinated subjects under 9 years of age and all subjects 9 years of age and older received 1 vaccination (QIVc or men ACWY) on Day 1. For subjects under 9 years of ages who had not been previously vaccinated, 2 vaccinations were administered; the comparator vaccine group received men ACWY on Day 1 followed by a saline placebo vaccine on Day 29, whereas the QIVc group received 2 QIVc vaccinations on Days 1 and 29.

VE estimates for the 2 to < 18 and 3 to < 18 years of age groups related to the secondary efficacy endpoints (RT-PCR-confirmed, culture-confirmed, matched) are also presented in Table 30. Additionally, VE estimates against culture-confirmed antigenically unmatched to the vaccine strains are included.

Secondary Efficacy Objective 1: Vaccine Efficacy for RT- PCR- or Culture-Confirmed Influenza Regardless of Antigenic Match – By Strain Type and Age. Out of the 539 subjects with a RT-PCR- or culture confirmed influenza caused by any Type A or Type B strain, there were 310 episodes caused by Type A and 231 caused by Type B.

Secondary Efficacy Objective 2: Vaccine Efficacy for RT- PCR-Confirmed Influenza Regardless of Antigenic Match. The estimates of the overall VE of QIVc against RT-PCR- or culture-confirmed influenza in comparison to the estimates of the overall VE against RT-PCR confirmed influenza are similar. The strain specific VE estimates differ slightly as the RT-PCR method was unable to determine the strain type

of 29 influenza Type A strains, and therefore there were fewer Type A/H1N1 and Type A/H3N2 results by this method.

Secondary Efficacy Objective 3: Vaccine Efficacy for Culture-Confirmed Influenza Regardless of Antigenic Match. In subjects 2 to < 18 and 3 to < 18 years of age, absolute vaccine efficacy of QIVc versus the comparator was demonstrated as determined by the first occurrence of culture-confirmed influenza due to any influenza Type A and B strains regardless of antigenic match. See Table 30.

Secondary Efficacy Objective 4: Vaccine Efficacy for Culture-Confirmed Influenza Antigenically Matched. In subjects 2 to < 18 years of age, absolute vaccine efficacy of QIVc versus the comparator was demonstrated as determined by the first occurrence of culture-confirmed influenza due to antigenically matched influenza Type A and B strains. No differences were observed between subjects 2 to < 18 years of age and 3 to < 18 years of age. See Table 30.

Table 30 Number of subjects with first-occurrence RT-PCR-Confirmed or Culture confirmed influenza and absolute vaccine efficacy (95% CI), overall and by strain, in subjects 2 to < 18 years of age and 3 to <18 years of age-FAS Efficacy

	2 to < 18 Years of Age[a]			3 to < 18 Years of Age[b]		
	QIVc N=2257 n (%)	Comparator N=2252 n (%)	aVE[c] (95% CI)	QIVc N=2208 n (%)	Comparator N=2201 n (%)	aVE[c] (95% CI)
RT-PCR or Culture Confirmed[2]						
Any Strain - Number of cases (attack rate)	**175 (7.8)**	**364 (16.2)**	**54.63 (45.67, 62.12)**	**171 (7.7)**	**351 (15.9)**	**54.03 (44.80, 61.71)**
Type A	96 (4.3)	214 (9.5)	56.97 (45.25, 66.18)	94 (4.3)	204 (9.3)	55.98 (43.78, 65.52)
A/H1N1	21 (0.9)	105 (4.7)	80.73 (69.21, 87.94)	20 (0.9)	97 (4.4)	80.38 (68.23, 87.88)
A/H3N2	60 (2.7)	102 (4.5)	42.08 (20.32, 57.89)	59 (2.7)	99 (4.5)	41.24 (18.89, 57.44)
Type B	81 (3.6)	150 (6.7)	47.62 (31.36, 60.03)	79 (3.6)	147 (6.7)	47.72 (31.27, 60.23)
RT-PCR Confirmed[2]						
Any Strain - Number of cases (attack rate)	**175 (7.8)**	**364 (16.2)**	**54.63 (45.67, 62.12)**	**171 (7.7)**	**351 (15.9)**	**54.03 (44.80, 61.71)**
Type A	96 (4.3)	214 (9.5)	56.97 (45.25, 66.18)	94 (4.3)	204 (9.3)	55.98 (43.78, 65.52)
A/H1N1	19 (0.8)	103 (4.6)	82.21 (70.96, 89.10)	18 (0.8)	96 (4.4)	82.17 (70.50, 89.23)
A/H3N2	59 (2.6)	100 (4.4)	41.87 (19.80, 57.86)	58 (2.6)	98 (4.5)	41.62 (19.22, 57.81)
Type B	81 (3.6)	150 (6.7)	47.62 (31.36, 60.03)	79 (3.6)	147 (6.7)	47.72 (31.27, 60.23)

	2 to < 18 Years of Age[a]			3 to < 18 Years of Age[b]		
	QIVc N=2257 n (%)	Comparator N=2252 n (%)	aVE[c] (95% CI)	QIVc N=2208 n (%)	Comparator N=2201 n (%)	aVE[c] (95% CI)
Culture Confirmed[3]						
Any Strain - Number of cases (attack rate)	**115 (5.1)**	**279 (12.4)**	**60.81 (51.30, 68.46)**	**113 (5.1)**	**268 (12.2)**	**59.88 (50.00, 67.80)**
A/H1N1	17 (0.8)	93 (4.1)	82.28 (70.27, 89.44)	16 (0.7)	85 (3.9)	81.95 (69.19, 89.42)
A/H3N2	43 (1.9)	75 (3.3)	43.43 (17.70, 61.12)	42 (1.9)	72 (3.3)	42.27 (15.53, 60.55)
Type B	56 (2.5)	112 (5.0)	51.18 (32.71, 64.58)	56 (2.5)	111 (5.0)	50.50 (31.73, 64.10)
Culture Confirmed[3]						
Matched Strain - Number of cases (attack rate)	**90 (4.0)**	**236 (10.5)**	**63.64 (53.64, 71.48)**	**89 (4.0)**	**225 (10.2)**	**62.30 (51.81, 70.51)**
A/H1N1	17 (0.8)	92 (4.1)	82.10 (69.95, 89.33)	16 (0.7)	84 (3.8)	81.75 (68.84, 89.31)
A/H3N2	20 (0.9)	36 (1.6)	45.54 (5.90, 68.48)	20 (0.9)	33 (1.5)	40.50 (-3.72, 65.78)
B/Yamagata	52 (2.3)	105 (4.7)	51.59 (32.50, 65.28)	52 (2.4)	104 (4.7)	50.87 (31.45, 64.78)
B/Victoria	2 (0.1)	4 (0.2)	NA (NA, NA)	2 (0.1)	4 (0.2)	NA (NA, NA)
Culture Confirmed[3]						
Unmatched Strain - Number of cases (attack rate)	**25 (1.1)**	**43 (1.9)**	**42.47 (5.81, 64.86)**	**24 (1.1)**	**43 (2.0)**	**44.52 (8.58, 66.33)**
A/H1N1	0 (0)	1 (0.0)	NA (NA, NA)	0 (0)	1 (0.0)	NA (NA, NA)
A/H3N2	23 (1.0)	39 (1.7)	41.68 (2.35, 65.16)	25 (1.1)	50 (2.3)	43.92 (5.41, 66.75)
Type B	2 (0.1)	3 (0.1)	NA (NA, NA)	2 (0.1)	3 (0.1)	NA (NA, NA)

Other Efficacy Endpoints

The exploratory evaluation of QIVc efficacy to prevent the 2 prespecified complications of influenza, pneumonia and otitis media, was inconclusive [LL of the 2-sided 95% CI encompassing zero]. Number of subjects with first occurrence pneumonia and otitis were derived from AE forms and reported as medically attended AE reported within 30 days after ILI onset. The VE of QIVc relative to non-influenza comparator to prevent all-cause pneumonia and all-cause otitis media was not statistically significant.

Table 31 Summary of vaccine efficacy for First-occurrence of all-cause pneumonia and otitis media occurring at > 14 days after the last vaccination AND until the end of the influenza season in subjects 2 to < 18 years of age-FAS efficacy.

2 to <18 Years of Age	QIVc (n[%])	Comparator (n[%])	aVE (95% CI)
	N=2257	N=2252	
All-Cause Pneumonia			
Number of cases (attack rate)	18 (0.8)	14 (0.6)	-28.61 (-158.60, 36.04)
All-Cause Otitis Media			
Number of cases (attack rate)	23 (1.0)	16 (0.7)	-45.09 (-174.72, 23.38)

Source: Table 14.2.0.7.1.1 and Table 14.2.0.7.1.2.

Immunogenicity Results

The immunogenicity objectives were evaluated using the immunogenicity subset of subjects. The analysis was based on the FAS Immunogenicity.

Secondary Primary objective:

The secondary immunogenicity objective was to characterize the immunogenicity of QIVc by hemagglutination inhibition (HI assay) 3 weeks after the last vaccination in a subset of 751 subjects 2 to < 9 years of age, who were enrolled in Season 2 (n=432) and Season 3 (n=319). From those, 721 (n=422 [Season 2]; n=299 [Season 3]) were included in the FAS Immunogenicity.

Immunogenicity was assessed at baseline (Day 1; all subjects in immunogenicity subset), at Day 22 (all "previously vaccinated" subjects receiving a single dose of the study vaccine), and at Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains using the HI assay.

The vaccine strain composition changed between seasons. Except for the Type A/H1N1 vaccine strain, all other vaccine strains (Type A/H3N2, Type B/Yamagata and Type B/Victoria) were updated. Therefore, all the immunogenicity results are presented by season, even in the case where the strain did not change (eg, A/H1N1). For each assay and strain, the following measures were derived: GMTs, GMR,

seroconversion rates, and the percentages of subjects with HI titres ≥1:40. Immunogenicity was analysed descriptively and no success criteria were applied.

HI Geometric Mean Titres and Geometric Mean Ratios

The GMTs at Days 1, and 22/50 and GMR by vaccine groups are presented in Table 32. The GMT showed that:

· Overall there were no differences in GMT at Day 1 between QIVc and comparator.
· Across seasons, the GMTs at Day 1 were lowest against Type B/Victoria and B/Yamagata compared to the Type A/H1N1 and Type A/H3N2.
· The GMTs at Day 1 against Type A/H1N1 and Type B/Victoria were comparable between Season 2 and 3.
· The GMTs at Day 1 against Type A/H3N2 were higher for Season 2 compared with Season 3 (prevaccination GMTs, Season 2: 97.02 [QIVc], 94.40 [comparator] versus Season 3: 20.85 [QIVc], 20.74 [comparator]).
· The GMTs at Day 1 against Type B/Yamagata were higher in Season 3 compared with Season 2 (prevaccination GMTs, Season 2: 10.87 [QIVc], 12.17 [comparator] versus Season 3: 23.98 [QIVc] and 27.33 [comparator]).

There was a robust and substantial immune response across the 2 seasons in subjects who received QIVc; even with seasonal differences in vaccine strains and baseline GMTs.

The GMR showed:

· The GMR obtained for QIVc were higher than those for the comparator, with the notable exception of A/H3N2 in Season 2. A potential explanation is provided later in this section in the paragraphs titled "Type A/H3N2 responses".
· GMRs for QIVc by season were 5.76 and 9.73 for A/H1N1, 1.74 and 4.14 for A/H3N2, 3.79 and 7.01 for B/Victoria, and 4.63 and 5.27 for B/Yamagata in Season 2 and Season 3, respectively (Table 32.
· GMR for the comparator ranged between 0.99 and 1.25.

Consistent with the GMT results, post-vaccination HI titres were significantly higher in the QIVc group versus the comparator group for all strains (Table 32). The results obtained for PPS Immunogenicity were consistent with results obtained in the FAS.

Percentage of Subjects with an HI Titre ≥1:40

Table 32 presents the proportion of subjects with HI titres ≥1:40 at Day 1 and Day 22/50 in the FAS Immunogenicity analysis.

· Overall, there were no differences in subjects with HI titres ≥1:40 at Day 1 between QIVc and the comparator.
· Across seasons, the percentage of subjects with HI titres ≥1:40 at Day 1 were lowest against Type B/Victoria and Type B/Yamagata compared to the Type A/H1N1 and Type A/H3N2.
· The percentage of subjects with HI titres ≥1:40 at Day 1 against Type A/H1N1 and Type B/Victoria were comparable between Season 2 and 3.
· The percentage of subjects with HI titres ≥1:40 at Day 1 against Type A/H3N2 were higher for Season 2 compared to Season 3 (percentage of subjects with HI titres ≥1:40 at Day 1, Season 2: 93.3% [QIVc], 91.5% [comparator] versus Season 3: 27.9% [QIVc], 26.9% [comparator]).
· The percentage of subjects with HI titres ≥1:40 at Day 1 against Type B/Yamagata were higher in Season 3 compared to Season 2 (percentage of subjects with HI titres ≥1:40 at Day 1, Season 2: 18.6% [QIVc], 20.3% [comparator] versus Season 3: 44.8% [QIVc], 49.0% [comparator]).
· The percentages of subjects that achieved a HI antibody titre ≥ 1:40 at Day 22/50 were higher in Season 3 (94.8% [Type A/H1N1], 74.0% [A/H3N2], 68.8% [Type B/Victoria] and 79.2% [B/Yamagata])

compared with Season 2 (88.6% [Type A/H1N1], 90.0% [A/H3N2], 54.3% [Type B/Victoria] and 63.8% [B/Yamagata]).
The results obtained for PPS Immunogenicity were consistent with results obtained in the FAS Immunogenicity.

Seroconversion Rate

Table 32 summarizes the seroconversion rate post-vaccination (21 days after last vaccination, eg, Day 22/50) in the FAS Immunogenicity.

The seroconversion rate in the QIVc group was higher as compared to the comparator group post-vaccination for all four strains. The LL of the 2-sided 95% CI for the proportion of subjects achieving an HI antibody seroconversion exceeded 30%, except for Type A/H3N2 in Season 2 (13.97%). The technical challenges with HI assay used to assess immunogenicity against A/Singapore/GP2050/2015 (H3N2) may have contributed to the reduced rates of seroconversion in Season 2 compared with the other strains (see explanation below).

Similar results were observed for subjects in the PPS Immunogenicity.

Type A/H3N2 responses

Differences in the immunological response measured by HI against Type A/H3N2 in Season 2 compared to Season 3 were noted, with nearly 4-fold higher baseline titre against Type A/H3N2 observed. In recent years, genetic changes in the HA of circulating and vaccine virus strains of A/H3N2 have resulted in the loss of capacity to agglutinate chicken or turkey erythrocytes (van Baalen et al. 2014). This was the case for the A/H3N2 strain used in the vaccine in Season 2 (A/Singapore/GP2050/2015) and thus the HI assay might not have reliably measured the immunogenicity against this virus strain. The HI assay in Season 2 used guinea pig red blood cells without oseltamivir. Under these testing conditions, hemagglutination was predominantly due to neuraminidase (NA) and therefore the assay has measured mostly anti-NA antibodies (Mögling et al. 2017). Therefore, the HI results observed in Season 2 for the A/H3N2 strains should be considered less reliable. In addition, the use of erythrocytes from different species in Seasons 2 and 3 might also explain the differences in baseline titres across these seasons (Makkoch et al. 2012, Trombetta et al. 2018).

In Season 3 the A/North Carolina 04/2016 (H3N2) vaccine strain regained the capacity for hemagglutination through HA and the testing was done using turkey RBCs, not guinea pig. The interpretation of the data should therefore be consistent with the standard HI assay (Ovsyannikova et al. 2014). Unfortunately, the A/North Carolina 04/2016 (H3N2) virus had an unusually low hemagglutination titre which appears to have reduced the sensitivity of the assay (more virus particles to make 1 hemagglutination unit) and may explain the low HI GMT postvaccination.

In light of the technical challenges with the HI assay, quantification of neutralizing antibody titres using the MN assay against Type A/H3N2 was used as an alternative. The MN assay was used to measure immunogenicity in this study as an exploratory endpoint.

Table 32 Postvaccination GMT, GMR, and percentage of subjects 2 to <9 years of age with seroconversion and HI titer ≥1:40, with 95% Cis, 21 days after last vaccination (day 22 or day 50)- FAS immunogenicity.

	Season 2		Season 3	
	QIVc No./%, (95% CI)	Comparator No./%, (95% CI)	QIVc No./%, (95% CI)	Comparator No./%, (95% CI)
A/H1N1	**N = 210**	**N = 212**	**N = 154**	**N = 145**
Day 1 HI GMT	50.83 (41.89, 61.66)	47.51 (39.15, 57.64)	36.62 (22.61, 59.31)	31.76 (19.88, 50.74)
Day 22/50 HI GMT	283.45 (249.22, 322.38)	49.20 (43.24, 55.98)	380.70 (283.12, 511.91)	48.22 (36.14, 64.32)
GMR HI Titer	5.76 (5.06, 6.55)	1.00 (0.88, 1.14)	9.73 (7.24, 13.09)	1.23 (0.92, 1.64)
Day 1 % HI Titer ≥40	61.4 (54.48, 68.05)	58.5 (51.54, 65.20)	57.1 (48.93, 65.08)	53.1 (44.65, 61.43)
Day 22/50 % HI Titer ≥40	88.6 (83.47, 92.54)	58.6 (51.59, 65.31)	94.8 (90.02, 97.73)	55.2 (46.70, 63.43)
Seroconversion rate (%) - HI Titer	59.5 (52.55, 66.22)	1.9 (0.52, 4.80)	74.0 (66.35, 80.75)	6.2 (2.88, 11.46)
A/H3N2	**N = 210**	**N = 212**	**N = 154**	**N = 145**
Day 1 HI GMT	97.02 (86.51, 108.81)	94.40 (84.19, 105.84)	20.85 (15.99, 27.20)	20.74 (16.02, 26.85)
Day 22/50 HI GMT	168.73 (150.87, 188.70)	96.27 (86.05, 107.70)	67.64 (57.03, 80.24)	16.73 (14.17, 19.77)
GMR HI Titer	1.74 (1.56, 1.95)	0.99 (0.89, 1.11)	4.14 (3.49, 4.91)	1.02 (0.87, 1.21)
Day 1 % HI Titer ≥40	93.3 (89.07, 96.31)	91.5 (86.91, 94.89)	27.9 (21.00, 35.71)	26.9 (19.88, 34.89)
Day 22/50 % HI Titer ≥40	90.0 (85.12, 93.70)	92.4 (87.92, 95.58)	74.0 (66.35, 80.75)	24.8 (18.03, 32.68)
Seroconversion rate (%) - HI Titer	19.0 (13.97, 25.02)	1.9 (0.52, 4.80)	51.9 (43.76, 60.06)	1.4 (0.17, 4.89)
B/Victoria	**N = 210**	**N = 212**	**N = 154**	**N = 145**
Day 1 HI GMT	11.67 (9.97, 13.67)	11.73 (10.02, 13.73)	9.54 (7.25, 12.54)	9.41 (7.22, 12.28)
Day 22/50 HI GMT	45.25 (39.73, 51.54)	11.94 (10.48, 13.60)	66.82 (51.29, 87.04)	11.94 (9.23, 15.44)
GMR HI Titer	3.79 (3.33, 4.32)	1.00 (0.88, 1.14)	7.01 (5.38, 9.14)	1.25 (0.97, 1.62)
Day 1 % HI Titer ≥40	25.2 (19.51, 31.68)	24.1 (18.47, 30.39)	13.6 (8.64, 20.09)	15.2 (9.76, 22.07)
Day 22/50 % HI Titer ≥40	54.3 (47.29, 61.16)	24.3 (18.65, 30.66)	68.8 (60.88, 76.04)	13.1 (8.08, 19.70)
Seroconversion rate (%) - HI Titer	40.0 (33.32, 46.97)	2.9 (1.06, 6.11)	58.4 (50.23, 66.32)	3.4 (1.13, 7.86)
B/Yamagata	**N = 210**	**N = 212**	**N = 154**	**N = 145**
Day 1 HI GMT	10.87 (9.46, 12.50)	12.17 (10.59, 13.99)	23.98 (16.74, 34.36)	27.33 (19.27, 38.76)
Day 22/50 HI GMT	52.81 (45.77, 60.94)	12.34 (10.68, 14.24)	108.49 (85.16, 138.22)	21.68 (17.11, 27.46)
GMR HI Titer	4.63 (4.01, 5.34)	1.08 (0.94, 1.25)	5.27 (4.14, 6.72)	1.05 (0.83, 1.33)
Day 1 % HI Titer ≥40	18.6 (13.55, 24.50)	20.3 (15.09, 26.33)	44.8 (36.80, 53.02)	49.0 (40.58, 57.39)
Day 22/50 % HI Titer ≥40	63.8 (56.91, 70.31)	21.4 (16.08, 27.60)	79.2 (71.95, 85.33)	46.2 (37.90, 54.67)
Seroconversion rate (%) - HI Titer	49.5 (42.57, 56.49)	4.8 (2.31, 8.58)	58.4 (50.23, 66.32)	1.4 (0.17, 4.89)

Table 33 Postvaccination GMT, GMT and Percentage of subjects 2 to <9 years of age with seroconversion, with 95% Cis, 21 days after last vaccination 9day 22 or day 50)-FAS immunogenicity NM

	Season 2		Season 3	
	QIVc No./%, (95% CI)	Comparator No./%, (95% CI)	QIVc No./%, (95% CI)	Comparator No./%, (95% CI)
A/H1N1	**N = 210**	**N = 212**	**N = 154**	**N = 145**
Day 1 MN GMT	133.51 (108.47, 164.32)	127.63 (103.83, 156.89)	26.26 (15.54, 44.38)	19.87 (11.93, 33.07)
Day 22/50 MN GMT	632.73 (527.05, 759.60)	124.57 (103.75, 149.57)	223.11 (160.71, 309.74)	24.67 (17.92, 33.95)
GMR MN Titer	4.93 (4.10, 5.91)	0.97 (0.81, 1.16)	8.42 (6.07, 11.69)	0.93 (0.68, 1.28)
Day 22/50 % 4-Fold Rise MN Titer	64.8 (57.89, 71.21)	8.6 (5.16, 13.21)	74.0 (66.35, 80.75)	5.5 (2.41, 10.58)
A/H3N2	**N = 210**	**N = 212**	**N = 154**	**N = 145**
Day 1 MN GMT	88.18 (71.50, 108.74)	107.42 (87.21, 132.30)	63.34 (39.37, 101.88)	55.75 (35.13, 88.46)
Day 22/50 MN GMT	301.47 (268.38, 338.64)	97.23 (86.55, 109.23)	375.40 (280.99, 501.54)	46.32 (34.97, 61.34)
GMR MN Titer	3.09 (2.75, 3.47)	1.00 (0.89, 1.12)	8.83 (6.61, 11.80)	1.09 (0.82, 1.44)
Day 22/50 % 4-Fold Rise MN Titer	42.9 (36.07, 49.85)	3.3 (1.35, 6.75)	77.9 (70.54, 84.20)	6.2 (2.88, 11.46)
B/Victoria	**N = 210**	**N = 212**	**N = 154**	**N = 145**
Day 1 MN GMT	19.73 (15.92, 24.46)	19.31 (15.60, 23.90)	86.72 (64.46, 116.66)	91.08 (68.27, 121.49)
Day 22/50 MN GMT	95.13 (83.15, 108.84)	20.22 (17.67, 23.13)	246.95 (193.15, 315.74)	86.59 (68.20, 109.95)
GMR MN Titer	4.75 (4.15, 5.44)	1.01 (0.88, 1.16)	2.83 (2.21, 3.62)	0.99 (0.78, 1.26)
Day 22/50 % 4-Fold Rise MN Titer	60.5 (53.52, 67.14)	1.0 (0.12, 3.40)	40.3 (32.45, 48.46)	4.8 (1.96, 9.69)
B/Yamagata	**N = 210**	**N = 212**	**N = 154**	**N = 145**
Day 1 MN GMT	10.87 (9.45, 12.51)	12.22 (10.63, 14.05)	78.08 (52.27, 116.64)	77.55 (52.51, 114.52)
Day 22/50 MN GMT	84.90 (73.65, 97.88)	11.56 (10.02, 13.33)	323.88 (243.21, 431.31)	66.92 (50.67, 88.40)
GMR MN Titer	7.50 (6.50, 8.64)	1.02 (0.89, 1.18)	4.90 (3.68, 6.52)	1.01 (0.77, 1.34)
Day 22/50 % 4-Fold Rise MN Titer	71.9 (65.31, 77.87)	1.4 (0.30, 4.12)	64.9 (56.84, 72.44)	10.3 (5.91, 16.49)

Study V130_10

Title of Study: "A Phase 3, Randomized, Observer-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of a Cell-based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) and a United States-licensed Quadrivalent Influenza Virus Vaccine (QIV) in Healthy Subjects 6 Months Through 47 Months"

Description

The purpose of this Phase 3, randomized, observer-blind, comparator-controlled, multicentre study of QIVc versus a US-licensed QIV was to evaluate the immunogenicity and safety of each of the 4 influenza strains contained in QIVc. Immunogenicity was evaluated at Day 1 and Day 29 (previously vaccinated subjects, 1 dose of vaccine) or Day 1 and Day 57 (not previously vaccinated subjects, 2 doses of vaccine). For the noninferiority assessment, immunogenicity was evaluated by measurement of serum hemagglutination inhibition (HAI) antibody titers for all influenza strains except A/H3N2.

Evolutionary changes in A/H3N2 HA protein have resulted in the loss of capacity to agglutinate red blood cells for recently circulating strains. Therefore, in consultation with Center for Biologics Evaluation and Research (CBER)/FDA prior to study initiation, it was decided to assess the 2 A/H3N2 co-primary endpoints using a microneutralization (MN) assay instead. The data from this study will be used to support the licensure of QIVc for use in children 6 months through 47 months of age.

Methods

Objective(s)

Primary Immunogenicity Objective

The primary immunogenicity objective was to demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a US-licensed QIV containing the recommended strains for the season, in subjects 6 months through 47 months of age, as measured by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for A/H3N2 strain, using cell-derived target viruses.

The criteria for concluding noninferiority of QIVc to the US-licensed QIV are as follows:

The noninferiority of QIVc compared with the US-licensed QIV was assessed by the 8 co-primary endpoints of GMT and SCR for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria.

Definitions for the noninferiority assessment based on endpoints measured by the HAI assay (GMT ratio <1.5 and SCR difference <10%) were derived from the FDA Guidance on seasonal inactivated influenza vaccines (CBER 2007). The definitions for the noninferiority assessment using endpoints measured by the MN assay were based on those used for the HAI assay. The study was to be considered successful if all 8 co-primary endpoints are achieved. Specifically, QIVc was to be considered to be noninferior to the US-licensed QIV if, for each of the 4 strains, the following statistical criteria were met:

A/H1N1, B/Yamagata, and B/Victoria

- The upper bound of the 2-sided 95% CI for the ratio of the HAI GMTs does not exceed 1.5. The HAI GMT ratio was calculated as HAI GMT (US-licensed QIV) divided by HAI GMT (QIVc).
- The upper bound of the 2-sided 95% CI for the difference between the HAI SCRs does not exceed 10%. The difference in HAI SCRs was calculated as HAI SCR (US-licensed QIV) minus HAI SCR (QIVc). The 95% CI was computed based on the binomial distribution.

A/H3N2 strain only

- The upper bound of the 2-sided 95% CI for the ratio of the MN GMTs does not exceed 1.5. The MN GMT ratio was calculated as MN GMT (US-licensed QIV) divided by MN GMT (QIVc).
- The upper bound of the 2-sided 95% CI for the difference between the MN SCRs does not exceed 10%. The difference in MN SCRs was calculated as MN SCR (US-licensed QIV) minus MN SCR (QIVc). The 95% CI was computed based on the binomial distribution.

<u>Secondary Immunogenicity Objective</u>

1. To describe the immunogenicity of QIVc and US-licensed QIV by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains, and by MN assay for A/H3N2 strain, using egg-derived target viruses
2. To describe the immunogenicity of QIVc and US-licensed QIV by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains, and by MN assay for A/H3N2 strain, using cell-derived target viruses
3. To describe the immunogenicity of QIVc and US-licensed QIV by MN assay for A/H1N1, B/Yamagata, and B/Victoria strains, in a subset of subjects

<u>Secondary Safety Objective</u>

The secondary safety objective was to evaluate the safety and reactogenicity of QIVc and US-licensed QIV.

Exploratory Immunogenicity Objectives

1. To evaluate the homologous cell-mediated immunity (CMI) response, prevaccination and postvaccination, in a small population of subjects
2. To further describe the immune response to vaccination, additional immunogenicity analyses may be conducted such as HAI assay for A/H3N2 using cell- and egg-derived target viruses

Study design

This study was designed as a Phase 3, randomized, observer-blind, comparator-controlled, multicenter study of QIVc versus US-licensed QIV in children 6 months through 47 months of age. Study vaccine administration was a single dose, or 2 doses 28 days apart, depending on the influenza vaccination history of the subject; previously vaccinated subjects received 1 dose and not previously vaccinated subjects received 2 doses. Study V130_10 was conducted during the Northern Hemisphere 2019/2020 influenza season.

The US-licensed QIV was Afluria Quadrivalent, which was administered according to the US Package Insert. The age indication for Afluria Quadrivalent was extended to include children 6 months through 59 months of age by the FDA in October 2018. Each vaccine contained the influenza strains recommended by the WHO for the influenza season covered by the study. The purpose of the study was to demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a US-licensed QIV in children 6 months through 47 months of age; therefore, a noninferiority study design was chosen.

The study comprised a treatment period and a follow-up period. The treatment period extended from the time of first vaccination to 28 days after the last vaccination; therefore, the duration of study participation was dependent upon the number of doses of vaccine that the subject received.

Study participation concluded with a Study Completion Call 180 days after the last vaccination.

Previously vaccinated subjects

- Treatment Period (Day 1 through Day 29):
    - 1 vaccination (QIVc or US-licensed QIV) on Day 1
- Follow-up Period (Day 29 through Day 181)

Not previously vaccinated subjects

- Treatment Period (Day 1 through Day 57):
    - 2 vaccinations (QIVc or US-licensed QIV) on Day 1 and Day 29
- Follow-up Period (Day 57 through Day 209)

The study vaccine (QIVc or the US-licensed QIV) was administered intramuscularly into the anterolateral region of the thigh (for subjects 6 months through 11 months, in general) or in the deltoid region (for subjects 12 months and older, in general). QIVc was administered as a 0.5 mL dose. The US-licensed QIV was administered following the dose recommendations described in the US Package Insert, ie, a 0.25 mL dose for subjects 6 months through 35 months of age and a 0.5 mL dose for subjects 36 months through 47 months of age.

After vaccination, all subjects remained under medical supervision and were monitored for any immediate postvaccination reactions (including solicited local and systemic AEs, unsolicited AEs, and body temperature measurement) for at least 30 minutes. The data collected during the 30-minute observation were recorded in the source documents only.

Solicited local adverse reactions and solicited systemic AEs were collected from 30 minutes after vaccination on a Subject Diary Card, and collection continued for a total of 7 days.

Parent(s)/LAR(s) received a reminder call to complete the Subject Diary Card 2 days after vaccination. The Subject Diary Card was the only source document allowed for solicited local adverse reactions and systemic AEs, including body temperature measurements. In children younger than 36 months of age, measurement of body temperature was preferably by the rectal route. Oral, axillary, or tympanic membrane routes could be used in older children.

All unsolicited AEs were collected during the treatment period. During the follow-up period, it was required to report only unsolicited AEs that were SAEs, NOCD, or AEs leading to withdrawal on the Adverse Events electronic Case Report Form (eCRF).

Subjects provided a serological specimen by a blood draw before vaccination on Day 1 and 28 days after the last vaccination during scheduled clinic visits:

- Previously vaccinated subjects provided a serological specimen on Day 1 and Day 29 (vaccination on Day 1)
- Not previously vaccinated subjects provided a serological specimen on Day 1 and Day 57 (vaccination on Day 1 and Day 29)

The serological specimen on the day of vaccination was obtained before vaccination.

Study population /Sample size

It was planned to conduct the study with approximately 2502 healthy male and female subjects who were 6 months through 47 months of age: 2418 subjects for evaluation of immunogenicity (Immunogenicity Group) and 84 subjects (24 months through 47 months of age) for exploratory evaluation of CMI (CMI Population). Stratification through Interactive Response Technology (IRT) was used to ensure a balanced distribution among the age groups; it was planned that at least 30% of subjects would be 6 months through 23 months of age and at least 30% of subjects would be 24 months through 47 months of age.

Subjects were enrolled into the study and randomized via an IRT system to receive QIVc or US-licensed QIV in a 2:1 ratio.

Inclusion Criteria

In order to participate in this study, all subjects must have met ALL of the inclusion criteria described below:

1. Individuals 6 through 47 months of age on the day of informed consent;
2. Individuals whose parent(s)/LAR(s) had voluntarily given written informed consent after the nature of the study had been explained according to local regulatory requirements, prior to study entry;
3. Individuals who could comply with study procedures, including follow-up; and
4. Individuals who were in generally good health as per the Investigator’s medical judgement.

Prior to receipt of second study vaccination, subjects must have been re-evaluated to confirm that they were eligible for subsequent vaccination. If subjects did not meet criteria 3 and/or 4 of the original inclusion criteria listed above, they should not have received additional vaccinations.

Exclusion Criteria

Each subject must not have had/been:

1. Acute (severe) febrile illness.
2. History of any anaphylaxis, serious vaccine reactions or hypersensitivity, including allergic reactions, to any component of vaccine or medical equipment whose use was foreseen in this study;
3. Clinical conditions representing a contraindication to intramuscular (IM) vaccination and blood draws. These may include known bleeding disorders, or treatment with anticoagulants in the 3 weeks preceding vaccination;
4. A known history of Guillain-Barre Syndrome or other demyelinating diseases such as

   encephalomyelitis and transverse myelitis;
5. Abnormal function of the immune system resulting from clinical conditions, including:

   a. Known or suspected congenital or acquired immunodeficiency

   b. Systemic administration of corticosteroids (PO/IV/IM) at any dose for more than 14 days, within 90 days prior to informed consent. Topical, inhaled and intranasal corticosteroids are permitted. Intermittent use (1 dose in 30 days) of intra-articular corticosteroids is also permitted

   c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent
6. Received immunoglobulins or any blood products within 180 days prior to informed consent;
7. Received an investigational or non-registered medicinal product within 30 days prior to informed consent, or intend to participate in another clinical trial during the study;
8. Study personnel, family and household members of study personnel should not participate;
9. Any other clinical condition that, in the opinion of the Investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study;
10. Received influenza vaccination or has had documented influenza disease in the last 6 months prior to informed consent; or
11. Received any other vaccines than influenza vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to study vaccination or who are planning to receive any vaccine within 28 days after study vaccination.

Treatments

Subjects in the QIVc group received a 0.5 mL IM dose of QIVc (1 or 2 doses, depending on influenza vaccination history).

Subjects in the US-licensed QIV comparator vaccine group who were:

- 6 months through 35 months of age received a 0.25 mL IM dose of the comparator vaccine (1 or 2 doses, depending on influenza vaccination history);
- 36 months through 47 months of age received a 0.5 mL IM dose of the comparator vaccine (1 or 2 doses, depending on influenza vaccination history).

Investigational Vaccine

QIVc:

QIVc is a cell-based quadrivalent inactivated subunit seasonal influenza vaccine manufactured by Seqirus. QIVc is composed of antigens from 4 different influenza strains, ie, 2 influenza A strains (A/H1N1 and A/H3N2) and 2 influenza B strains (B/Yamagata and B/Victoria).

An approximately 0.5 mL dose of QIVc (cell-based quadrivalent subunit influenza virus vaccine; supplied in a 0.5 mL prefilled syringe) contains nominally 15 µg of HA of each of the 2 influenza Type A strains and each of the 2 influenza Type B strains for a total of 60 µg of HA in the vaccine. The strain composition was that recommended by the WHO, CBER, and Committee for Medicinal Products for Human Use (CHMP) for quadrivalent influenza vaccines contemporaneous to the timing of the study. The full composition of the vaccine is reported in

Table 34 below. The product lot number of QIVc used in the study was 261303 (expiry date: 19 June 2020).

Table 34 QIVc Vaccine composition

Names of Ingredients	Quantity per dose (0.5 mL/dose)[a]	Function
Active Ingredients Hemagglutinin and neuraminidase antigens from the influenza virus strains recommended by the WHO/CBER/CHMP for the respective season. • A/Idaho/07/2018 (A/H1N1) • A/Indiana/08/2018 (A/H3N2) • B/Singapore/INFTT-16-0610/2016 (B/Yamagata) • B/Iowa/06/2017 (B/Victoria)	15 µg HA (per strain)	Influenza vaccine

Abbreviations: CBER=Center for Biologics Evaluation and Research; CHMP=Committee for Medicinal Products for Human Use; DNA=deoxyribonucleic acid; HA=hemagglutinin; MDCK=Madin-Darby Canine Kidney

[a] The quantities indicated in this table reflect the amount in a 0.5 mL dose.

US-licensed QIV comparator vaccine

Afluria Quadrivalent inactivated influenza virus vaccine

The US-licensed QIV comparator vaccine was Afluria Quadrivalent, an inactivated quadrivalent influenza vaccine composed of antigens from 4 different influenza strains, ie, 2 influenza A strains (A/H1N1 and A/H3N2) and 2 influenza B strains (B/Yamagata and B/Victoria). The strain composition of Afluria Quadrivalent used in this study is provided in Table 35

Afluria Quadrivalent was administered following the dose recommendations described in the US Package Insert. Afluria Quadrivalent is supplied in a 0.25 mL and a 0.5 mL prefilled syringe. For children 6 months through 35 months of age, 0.25 mL dose of vaccine was administered. For children 36 months through 47 months of age, 0.5 mL was administered. The strain composition was that recommended by the WHO, CBER, and CHMP for quadrivalent influenza vaccines contemporaneous to the timing of the study. The full composition of the vaccine is reported in Table 35. The product lot numbers of Afluria Quadrivalent used in the study were P100100543 (expiry date: 16 May 2020) for the 0.5 mL dose and P100118460 (expiry date: 30 June 2020) and P100114135 (expiry date: 30 June 2020) for the 0.25 mL dose.

Table 35 Afluria quadrivalent vaccine composition

Names of Ingredients	Quantity per dose (0.5 mL/dose)[a]	Function
Active Ingredients Hemagglutinin and neuraminidase antigens from the influenza virus strains recommended by the WHO/CBER/CHMP for the respective season.	15 µg HA (per strain)	Influenza vaccine

• A/Brisbane/02/2018 (IVR-190) (A/H1N1) • A/Kansas/14/2017 (X-327) (A/H3N2) • B/Phuket/3073/2013 (BVR-1B) (B/Yamagata) • B/Maryland/15/2016 (B/Victoria)		

Abbreviations: CBER=Center for Biologics Evaluation and Research; CHMP=Committee for Medicinal Products for Human Use; HA=hemagglutinin;

[a] The quantities indicated in this table reflect the amount in a 0.5 mL dose.

Outcomes/endpoints

Co-Primary Immunogenicity Endpoints

The co-primary endpoints were:

- Serum HAI antibody titer against A/H1N1, B/Yamagata, and B/Victoria vaccine strains at Day 29/57, using cell-derived target viruses:
    - GMT by HAI assay

      SCR defined as the percentage of subjects with either a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40, or a prevaccination HAI titer ≥1:10 and a ≥4- fold increase in postvaccination HAI titer
- Serum neutralizing antibody titer against A/H3N2 vaccine strain at Day 29/57, using cell-derived target viruses:
    - GMT by MN assay
    - SCR defined as the percentage of subjects with either a prevaccination MN titer <1:10 and a postvaccination MN titer ≥1:40, or a prevaccination MN titer ≥1:10 and a ≥4-fold increase in postvaccination MN titer
- Derived variables:
    - The GMT ratio (US-licensed QIV/QIVc) for each strain
    - The inter-group difference in the SCRs (US-licensed QIV minus QIVc) for each strain

The noninferiority of QIVc compared with US-licensed QIV was assessed for the following 8 co-primary endpoints of GMT and SCR for each cell-derived target virus strain included in QIVc as follows:

- The GMT ratio for the A/H1N1 strain (HAI assay)
- The GMT ratio for the A/H3N2 strain (MN assay)
- The GMT ratio for the B/Yamagata strain (HAI assay)
- The GMT ratio for the B/Victoria strain (HAI assay)
- The difference between the SCRs for the A/H1N1 strain (HAI assay)
- The difference between the SCRs for the A/H3N2 strain (MN assay)

- The difference between the SCRs for the B/Yamagata strain (HAI assay)
- The difference between the SCRs for the B/Victoria strain (HAI assay)

Secondary Immunogenicity Endpoints

1. Humoral immune response in terms of HAI antibodies against A/H1N1, B/Yamagata, and B/Victoria strains, using cell- and egg-derived target viruses:
    - GMT by HAI assay at Days 1 and 29/57
    - Geometric mean ratio (GMR), defined as the fold increase in serum HAI GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
    - Seropositivity rates (percentages of subjects with HAI titer ≥1:10) at Days 1 and 29/57
    - Percentages of subjects with HAI titer ≥1:40 at Days 1 and 29/57
    - SCR by HAI assay

Derived variables:

- The GMT ratio (US-licensed QIV/QIVc) for each strain
- The inter-group difference in the SCRs (US-licensed QIV minus QIVc) for each strain

2. Neutralizing antibody titers against A/H3N2 vaccine strains, using cell- and egg-derived target viruses:
    - GMT by MN assay at Days 1 and 29/57
    - GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
    - Seropositivity rates (percentages of subjects with MN titer ≥1:10 [lower limit of quantification (LLOQ)]) at Days 1 and 29/57
    - SCR by MN assay

Derived variables:

- The GMT ratio (US-licensed QIV/QIVc) for each strain
- The inter-group difference in the SCRs (US-licensed QIV minus QIVc) for each strain

3. Neutralizing antibody titers against A/H1N1, B/Yamagata, and B/Victoria vaccine strains, in a subset of subjects:
    - GMT by MN assay at Days 1 and 29/57
    - GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
    - Seropositivity rates (percentages of subjects with MN titer ≥1:10 [LLOQ]) at Days 1 and 29/57
    - SCR by MN assay

Derived variables:

- The GMT ratio (US-licensed QIV/QIVc) for each strain

- The inter-group difference in the SCRs (US-licensed QIV minus QIVc) for each strain

Secondary Safety Endpoints

The endpoints for assessment of safety and reactogenicity were:

1. Percentage of subjects with solicited adverse events (AEs) within 7 days after each study vaccination
2. Percentage of subjects with any unsolicited AEs from Day 1 to Day 29 (in previously vaccinated subjects) and from Day 1 to Day 57 (in not previously vaccinated subjects)
3. Percentage of subjects with any SAEs, New Onset of Chronic Disease (NOCD), or AEs leading to withdrawal during the entire study period (ie, from Day 1 to Day 181 for previously vaccinated subjects or from Day 1 to Day 209 for not previously vaccinated subjects)

Exploratory Immunogenicity Endpoints

1. CMI response to vaccination
   - Measurement of antigen-stimulated CD4+ T-cell responses via expression of cytokines
   - Measurement of antigen-stimulated CD8+ T-cell responses via expression of cytokines
2. Humoral immune response in terms of HAI antibodies against A/H3N2, using cell- and egg-derived target viruses:
   - GMT by HAI assay at Days 1 and 29/57
   - GMR, defined as the fold increase in serum HAI GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
   - Seropositivity rates (percentages of subjects with HAI titer ≥1:10) at Days 1 and 29/57
   - Percentages of subjects with HAI titer ≥1:40 at Days 1 and 29/57
   - SCR by HAI assay

   Derived variables:
   - The GMT ratio (US-licensed QIV/QIVc) for each strain
   - The inter-group difference in the SCRs (US-licensed QIV minus QIVc) for each strain

Statistical Methods

Descriptive statistics were used to present all safety and immunogenicity results: number of observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max) for continuous data and frequency and percentage relative to the appropriate population for categorical data.

Binary data (ie, percentages of subjects with SCR) were summarized for each group using unadjusted estimates and are reported together with 2-sided exact 95% CIs (Clopper-Pearson).

The difference between the proportions of treatment groups was determined and the corresponding 2-sided 95% CIs calculated by Miettinen-Nurminen method.

Geometric means and 95% CIs were calculated by taking the anti-logs of the means and 95% CI of the log transformed immunogenicity parameters. Exact CIs based upon the binomial distribution were calculated for percentages.

Statistical Hypothesis

The primary immunogenicity objective was to demonstrate that vaccination with QIVc elicited an immune response that was not inferior to that of a US-licensed QIV containing the recommended strains for the season, in subjects 6 months through 47 months of age, as measured by the HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains and by the MN assay for the A/H3N2 strain, using cell-derived target viruses.

The noninferiority of QIVc compared with the US-licensed QIV was assessed by the 8 co-primary endpoints of GMT and SCR for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria. Definitions for the noninferiority assessment based on endpoints measured by the HAI assay (GMT ratio <1.5 and SCR difference <10%) were derived from the FDA Guidance on seasonal inactivated influenza vaccines (CBER 2007). The definitions for the noninferiority assessment using endpoints measured by the MN assay were based on those used for the HAI assay. The study was to be considered successful if all 8 co-primary endpoints are achieved. Specifically, QIVc was to be considered to be noninferior to the US-licensed QIV if, for each of the 4 strains, the following statistical criteria were met:

A/H1N1, B/Yamagata, and B/Victoria

- The upper bound of the 2-sided 95% CI for the ratio of the HAI GMTs does not exceed 1.5. The HAI GMT ratio was calculated as HAI GMT (US-licensed QIV) divided by HAI GMT (QIVc).
- The upper bound of the 2-sided 95% CI for the difference between the HAI SCRs does not exceed 10%. The difference in HAI SCRs was calculated as HAI SCR (US-licensed QIV) minus HAI SCR (QIVc). The 95% CI was computed based on the binomial distribution.

A/H3N2 strain only

- The upper bound of the 2-sided 95% CI for the ratio of the MN GMTs does not exceed 1.5. The MN GMT ratio was calculated as MN GMT (US-licensed QIV) divided by MN GMT (QIVc).
- The upper bound of the 2-sided 95% CI for the difference between the MN SCRs does not exceed 10%. The difference in MN SCRs was calculated as MN SCR (US-licensed QIV) minus MN SCR (QIVc). The 95% CI was computed based on the binomial distribution.

Results

Recruitment/ number analysed

The size of the study population was consistent with the planned number of approximately 2502 subjects. A total of 2414 subjects 6 months through 47 months of age were enrolled in the study (All Enrolled Set) and randomized to receive QIVc or the US-licensed QIV. Twelve enrolled subjects did not receive study vaccine; thus, the FAS included 2402 subjects who received at least 1 study vaccination. Subjects were randomized to receive QIVc or the US licensed QIV in a 2:1 ratio as planned, with 1597 subjects receiving QIVc and 805 subjects receiving the US-licensed QIV. Of the 2402 subjects in the FAS, 2322 subjects were enrolled for evaluation of immunogenicity (Immunogenicity Group) and 80 subjects were enrolled for exploratory evaluation of CMI (CMI Population).

The majority of subjects (86.2%) completed the study; 334 of 2414 subjects (13.8%) discontinued from the study. The most common reason for discontinuing from the study was lost to follow-up (11.1% of subjects).

Baseline data

This study was conducted at 47 centers in the US. Demographic and baseline characteristics of the FAS (subjects in both the Immunogenicity Group and CMI Population) are summarized in Table 36, Demographics and baseline characteristics (full analysis set).

The mean (SD) age of the study population was 28.1 (11.57) months and the range was 6 months to 47 months of age, which was consistent with the intended study population. The stratification strategy was designed to ensure a balanced distribution among age groups such that at least 30% of subjects would be 6 months through 23 months of age and at least 30% of subjects would be 24 months through 47 months of age. The resulting age distribution met this intention, with 37.2% of subjects being 23 months of age or younger and 62.8% of subjects being 24 months of age or older.

The demographic characteristics were generally balanced between the QIVc group and US-licensed QIV group.

Table 36 Demographics and baseline characteristics (full analysis set)

	QIVc (N=1597) n (%)	US-licensed QIV (N=805) n (%)	Total (N=2402) n (%)
Age (months)			
n	1597	805	2402
Mean (SD)	28.1 (11.54)	28.2 (11.63)	28.1 (11.57)
Min, max	6, 47	6, 47	6, 47
Age group (n [%])			
n	1597	805	2402
6 months to 23 months	595 (37.3)	299 (37.1)	894 (37.2)
24 months to 47 months	1002 (62.7)	506 (62.9)	1508 (62.8)
Sex (n [%])			
n	1597	805	2402
Male	803 (50.3)	406 (50.4)	1209 (50.3)
Female	794 (49.7)	399 (49.6)	1193 (49.7)
Race (n [%])			
n	1597	805	2402
White	1039 (65.1)	539 (67.0)	1578 (65.7)
Black or African American	455 (28.5)	209 (26.0)	664 (27.6)
Asian	13 (0.8)	8 (1.0)	21 (0.9)
Native Hawaiian or Other Pacific Islander	8 (0.5)	6 (0.7)	14 (0.6)
American Indian or Alaska Native	11 (0.7)	11 (1.4)	22 (0.9)
Other	71 (4.4)	32 (4.0)	103 (4.3)
Ethnic origin (n [%])			
n	1597	805	2402
Hispanic or Latino	434 (27.2)	226 (28.1)	660 (27.5)
Not Hispanic or Latino	1160 (72.6)	575 (71.4)	1735 (72.2)
Not reported	3 (0.2)	3 (0.4)	6 (0.2)
Unknown	0	1 (0.1)	1 (<0.1)
Previous influenza vaccination (n [%])			
n	1597	805	2402
Previously vaccinated	810 (50.7)	430 (53.4)	1240 (51.6)
Not previously vaccinated	787 (49.3)	375 (46.6)	1162 (48.4)
Body mass index (kg/m^2)			
n	1596	805	2401
Mean (SD)	16.99 (2.466)	17.15 (2.996)	17.05 (2.656)
Median	16.73	16.75	16.74

Source: Table 14.1.1.3.2 and Listing 16.2.4.1.
Abbreviations: QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SD = standard deviation; US = United States.

Efficacy/immunogenicity results

In this study, the efficacy has been assessed in terms of immunogenicity.

The primary immunogenicity objective was to demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a US-licensed QIV containing the recommended strains for the season, in subjects 6 months through 47 months of age, as measured by HAI assay for A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for A/H3N2 strain, using cell-derived target viruses.

The prespecified noninferiority criterion for the GMT ratio (adjusted analysis) was met for all 4 strains contained in the QIVc vaccine:

- The upper bound of the 2-sided 95% CI for the GMT ratios (US-licensed QIV/QIVc) did not exceed the prespecified noninferiority margin of 1.5 (A/H1N1: 0.836; A/H3N2: 1.160; B/Yamagata: 0.809; B/Victoria: 0.972).

Table 37 Postvaccination GMT, GMT ratio, and analysis of noninferiority of QIVc relative to US-licensed QIV and subjects of 6 months through 47 months of age for A/H1N1, B/Yamagata, and B/Victoria (HAY assay data) and A/H3N2 (MN assay data), using cell-derived target viruses-per protocol set, study V130_10

	Day 29/57 GMT		GMT Ratio	
	QIVc N_{HAI}=1092 / N_{MN}=1078 (95% CI)	US-licensed QIV N_{HAI}=575 / N_{MN}=572 (95% CI)	US-licensed QIV over QIVc (95% CI)	Met predefined noninferiority criteria?
A/H1N1	78.0 (70.75, 86.03)	57.3 (50.76, 64.63)	0.73 (0.645, **0.836**)	Yes
A/H3N2	23.1 (21.21, 25.12)	23.9 (21.57, 26.57)	1.04 (0.927, **1.160**)	Yes
B/Yamagata	35.6 (32.93, 38.58)	26.0 (23.54, 28.63)	0.73 (0.656, **0.809**)	Yes
B/Victoria	22.4 (20.70, 24.19)	19.6 (17.81, 21.58)	0.88 (0.791, **0.972**)	Yes

Source: CSR V130_10, Table 11-1.

Abbreviations: CI = confidence interval; GMT = geometric mean titer; HAI = hemagglutination inhibition; MN = microneutralization; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; US = United States.

Note 1: Immunogenicity measured by HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for the A/H3N2 strain. N_{HAI} = number of subjects with valid HAI assay results; N_{MN} = number of subjects with valid MN assay results.

Note 2: Immunogenicity measured using cell-derived target virus in both the HAI and MN assays. The cell-derived target viruses were A/Idaho/07/2018 (A/H1N1), A/Indiana/08/2018 (A/H3N2), B/Singapore/INFTT-16-0610/2016 (B/Yamagata), and B/Iowa/06/2017 (B/Victoria).

Note 3: Adjusted GMT and GMT ratio are presented.

Note 4: Adjusted analysis GMT model: Log-transformed Postvaccination HAI (or MN) Titer = Vaccine + Age Strata + Gender + Vaccination History [y/n] + Log-transformed Prevaccination HAI (or MN) Titer + Site + Age Strata*Vaccine.

Note 5: Noninferiority criterion for the GMT ratio: upper bound of the 2-sided 95% CI on the GMT ratio of US-licensed QIV over QIVc does not exceed 1.5.

The prespecified noninferiority criterion for the SCR difference in subjects was met for all 4 strains contained in the QIVc vaccine:

- The upper bound of the 2-sided 95% CI for the SCR differences (US-licensed QIV minus QIVc) did not exceed the prespecified noninferiority margin of 10% (A/H1N1: -6.423%; A/H3N2: 7.812%; B/Yamagata: -9.983%; B/Victoria: -1.440%).

Table 38 SCR, SCR difference, and analysis of noninferiority of QIVc relative to US-licensed QIV in subjects of 6 months through 47 months of age for A/H1N1, B/Yamagata, and B/Victoria (HAI assay data) and A/H3N2 (MN assay data), using cell-derived target viruses-per protocol set, study V130_10

	SCR		SCR Difference	
	QIVc N_{HAI}=1092 / N_{MN}=1078 % (95% CI)	**US-licensed QIV N_{HAI}=575 / N_{MN}=572 % (95% CI)**	**US-licensed QIV minus QIVc % (95% CI)**	**Met predefined noninferiority criteria?**
A/H1N1	58.24 (55.25, 61.19)	46.78 (42.64, 50.96)	-11.46 (-16.447, -**6.423**)	Yes
A/H3N2	27.64 (24.99, 30.42)	30.77 (27.01, 34.73)	3.13 (-1.443, **7.812**)	Yes
B/Yamagata	46.52 (43.53, 49.53)	31.65 (27.87, 35.63)	-14.87 (-19.610, -**9.983**)	Yes
B/Victoria	30.31 (27.60, 33.13)	24.35 (20.89, 28.07)	-5.96 (-10.327, **-1.440**)	Yes

Source: CSR V130_10, Table 11-2.

Abbreviations: CI = confidence interval; HAI = hemagglutination inhibition; MN = microneutralization; QIV = quadrivalent influenza vaccine; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SCR = seroconversion rate; US = United States.

Note 1: Immunogenicity measured by HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for the A/H3N2 strain. N_{HAI} = number of subjects with valid HAI assay results; N_{MN} = number of subjects with valid MN assay results.

Note 2: Immunogenicity measured using cell-derived target virus in both the HAI and MN assays. The cell-derived target viruses were A/Idaho/07/2018 (A/H1N1), A/Indiana/08/2018 (A/H3N2), B/Singapore/INFTT-16-0610/2016 (B/Yamagata), and B/Iowa/06/2017 (B/Victoria).

Note 3: Noninferiority criterion for the SCR difference: upper bound of the 2-sided 95% CI on the SCR difference for US-licensed QIV minus QIVc does not exceed 10%.

As all 8 co-primary immunogenicity endpoints were met, noninferiority of QIVc compared with the US-licensed QIV was concluded.

The immunogenicity results obtained in the PPS for the primary objective were supported by those obtained in the FAS Immunogenicity.

The secondary immunogenicity objectives were to describe the immunogenicity of QIVc and the US-licensed QIV by HAI and MN assays in subjects 6 months through 47 months of age, using egg-derived and cell-derived target viruses.

For evaluation of immunogenicity using egg-derived target viruses as measured by HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for the A/H3N2 strain, there were no notable differences in the immunogenicity endpoints between QIVc and the US-licensed QIV for all 4 vaccine strains.

For evaluation of immunogenicity using cell-derived target viruses as measured by HAI assay for the A/H1N1, B/Yamagata, and B/Victoria strains and by MN assay for the A/H3N2 strain, there were no notable differences in the immunogenicity endpoints between QIVc and the US-licensed QIV for the A/H3N2 and B/Victoria strains. For the A/H1N1 and B/Yamagata strains, the postvaccination immunogenicity endpoints were observed to be higher for QIVc than the US-licensed QIV for the Day 29/57 GMT, GMR, Day 29/57 percentage of subjects with titer >1:40, and SCR. A secondary objective was also to assess, in a randomly selected subset of subjects from the Immunogenicity Group, the immune responses to A/H1N1, B/Yamagata, and B/Victoria as measured in MN assays using cell-derived target viruses. This evaluation showed that there were no notable differences in the immunogenicity endpoints between the QIVc and US-licensed QIV groups for all 3 strains.

Overall, subgroup analyses stratified by prevaccination titer, influenza vaccination history, age, gender, and race showed that similar immune responses were elicited to QIVc and the US-licensed QIV.

One exploratory objective was to describe the immunogenicity of A/H3N2 for QIVc and the US-licensed QIV as measured by the HAI assay, using cell-derived and egg-derived target viruses. In the assay using cell-derived target viruses, there were no notable differences in the Day 1 GMTs, GMRs, seropositivity rates, and percentage of subjects with GMT titers ≥1:40 between the 2 vaccines, while the Day 29/57 GMT and SCR were observed to be higher for QIVc than the US-licensed QIV. There were no notable differences in Day 1 and Day 29/57 GMTs, GMRs, seropositivity rates, percentage of subjects with HAI titer ≥1:40, and SCRs between the 2 vaccines using egg-derived target viruses.

The other exploratory immunogenicity objective was to evaluate the CMI response in subjects 24 months through 47 months of age vaccinated with QIVc or the US-licensed QIV (CMI Population). Peripheral blood CD4+ and CD8+ T-cells responsive to influenza antigen stimulation in vitro, as measured by antigen-induced expression of markers of T-cell activation, were detected at low frequencies in subjects vaccinated with QIVc or the US-licensed QIV.

In summary, the primary objective of the study was achieved. QIVc was found to elicit an immune response in subjects 6 months through 47 months of age that was not inferior to the immune response elicited by a US-licensed QIV.

Study V58P13

Title of study: A Phase III, Randomized, Observer-Blind, Placebo-Controlled, Multicenter Study to Assess Clinical Efficacy of a Cell-Derived Subunit Influenza Vaccine and an Egg-Derived Subunit Influenza Vaccine in the 2007-2008 Influenza Season in Healthy Adult Subjects

Description

Study V58P13 is a phase III, three armed randomized, observer-blind, placebo-controlled, multi-center study performed over a period of approximately 9 months at multiple study sites in the US, Poland, and Finland.

Methods

Study participants

Subjects aged 18-49 were eligible to participate in this study. Persons with underlying health issues for which influenza vaccination is recommended according to the ACIP criteria or had laboratory confirmed influenza during the 6 months prior to vaccination were excluded. Moreover, persons hypersensitive to eggs or any substance within the vaccines, with a history of Guillain-Barré syndrome, anaphylaxis or serious reaction following vaccination, pregnant or breastfeeding or with acute illness within 3 days prior to the start of study were excluded.

Treatments

- One 0.5mL dose of cell culture-derived influenza vaccine containing the purified viral envelope-glycoproteins, neuraminidase (NA) and hemagglutinin (HA) [including 15µg of HA for each strain (A/Solomon Islands/3/2006 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/ 2506/2004-like)] recommended for the 2007-2008 influenza season in the Northern Hemisphere;

- One 0.5mL dose of the trivalent egg-derived influenza vaccine containing the purified viral envelope-glycoproteins neuraminidase (NA) and hemagglutinin (HA) [including 15µg of HA for each strain (A/Solomon Islands/3/2006 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/ 2506/2004-like)] recommended for the 2007-2008 influenza season in the Northern Hemisphere;
- One 0.5 mL IM dose of phosphate buffered solution (PBS).

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 dose of 0.5 ml.

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 the evaluation of protection against lab-confirmed ILI regardless of antigenic matching and of protection against "dissimilar" strains; the evaluation of 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 finally to evaluate the effect on the number of days of usual activity lost.

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

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.

The CDC-case definition of influenza like illness was applied, which is a fever of ≥37.8°C and cough or sore throat. 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. 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.

Immunogenicity

Secondary immunogenicity outcomes were: seroprotection at D22 (3 weeks after vaccination) and seroconversion at D22 (3 weeks after vaccination). In addition GMTs at day 1 and day 22 were determined and the geometric mean ratio was determined (D22/D1). Immunogenicity was determined by HI test performed by Clinical Serology Laboratory, Novartis Vaccines, Marburg, Germany.

Safety

Study subjects were observed in the clinic for 30 minutes after each vaccination for all immediate reactions. Local and systemic reactions as well as all AEs (including SAEs, onset of chronic illness and AEs resulting in withdrawal from the study) were collected from day 1 to day 7. From day 8 to day 22, all SAEs, onset of chronic illness, AEs necessitating a physician consultation and AEs resulting in withdrawal from the study were collected. From day 22 until study termination, all SAEs, onset of chronic illness, and AEs resulting in withdrawal from the study were collected.

Sample size

Assuming 11,700 subjects enrolled and randomized at a 1:1:1 ratio to receive the cell culture-derived influenza vaccine, egg-derived influenza vaccine or placebo, VE of 70%, 3% attack rate for influenza, and one-sided alpha equal to 0.0125, the power to reject each of the null hypotheses (for the cell culture-derived and for the egg-derived vaccines) is 92%. For purposes of the sample size and power calculations, to adjust for this double comparison, the conservative Bonferroni method was used to estimate the power; therefore, the alpha level for each comparison was set as alpha/2 (i.e., one-sided alpha equal to 0.0125).

VE* Cell culture-derived or Egg-derived Vaccine%	Attack Rate %	Power %
60	1	16
70	1	40
80	1	74
90	1	95
60	3	50
70	3	92
80	3	>99
90	3	>99
60	5	76
70	5	>99
80	5	>99
90	5	>99

Poisson method

Immunogenicity (HI titres) was determine in a subset of individuals: 240 in the CCI arm and 750 in the IVV arm. With 240 evaluable subjects in the cell culture-derived influenza vaccine group, the lower limits of the two-sided 95% CIs around the estimated percentage of subjects seroprotected or achieving seroconversion for HI antibody at day 22 would mtet or exceed the threshold levels of 70% and 40%, respectively, if seroprotection is at least 76% (95% CI, 70% - 83%), and the percentage of subjects with seroconversion in HI titer is at least 46.5% (95% CI, 40% - 54%).

Randomisation

Subjects were randomly allocated to the CCI arm, IVV arm or placebo arm in a 1:1:1 ratio. To support the IVV licensure, the first 1045 subjects enrolled and randomized at the US sites were included in the immunogenicity subset according to an unbalanced randomization ratio of 8:25:2 to receive the CCI (240 subjects), IVV (746 subjects), and placebo (59 subjects).

Blinding (masking)

The study was designed as observer-blind study

Statistical methods

The estimate of VE relative to placebo of each influenza vaccine for preventing virus-confirmed symptomatic influenza A or B illness, defined as influenza wild type strains antigenically similar to those contained in the vaccines was calculated.

Each vaccine was considered statistically compliant with the May 2007 CBER guidance for industry criteria for estimating VE against placebo if the lower limit of the one-sided simultaneous 97.5% Confidence Interval (CI) for the estimate of VE relative to placebo was greater than 40%.

Summary statistics (mean, median, min, max) for the number of days in bed associated with cases of virus-confirmed influenza, the number of inpatient and outpatient medical visits due to influenza illness or symptoms of influenza, and the number of days of usual activity that were lost due to influenza disease were calculated and compared between each influenza vaccine group and placebo using an analysis of variance (ANOVA) having factors for vaccine group and study region (Europe versus US). Two-sided adjusted p-values from Dunnett's test comparing the CCI least squares (LS) mean to the Placebo LS mean and comparing the IVV LS mean to the Placebo LS mean using the estimate of error from the ANOVA were constructed.

A suitable Bonferroni-like multiple comparison method was used to determine the necessary α required to control the overall Type I error rate in constructing each confidence interval for the estimate of the cell-culture -derived influenza VE relative to placebo and the egg-derived VE relative to placebo.

Results

Participant flow

A total of 11404 subjects were enrolled and randomized into three groups, 3828 received the CCI vaccine, 3676 received the IVV and 3900 received placebo. Overall 10844 subjects completed the study.

Recruitment

The first subject was enrolled on the 9th of October 2007. The last subject completed the study on the 8th of July 2008.

Conduct of the study

CCI vaccine group

A total of 526 subjects in the CCI vaccine group had protocol deviations. Some of the major reasons for protocol deviations were: visit 3 was done outside the window period (46.49%); subjects were lost to follow-up (33.27%); subjects had not undergone visit 3 (4.56%); vital signs were not measured at all time points (3.42%), subjects had been given a memo (listing changes to the Informed Consent Form (IFM)) that was not Institutional Review Board (IRB) approved (3.42%), and for 14 subjects (2.66%), ILI had been reported but swab collection was not done.

IVV group

In total 503 subjects in IVV group showed protocol deviations. Some of the major reasons for protocol deviations were -visit 3 was done outside the window period (49.5%); subjects were lost to follow-up (28.43%); blood had been drawn outside the window period (4.97%); subjects did not provide serum sample at visit 3 (4.17%).

Placebo group

In total 555 subjects in placebo group showed protocol deviations. Some of the major reasons for protocol deviations were -visit 3 was done outside the window period (49.37%); subjects were lost to follow-up (30.63%); subjects had not undergone visit 3 (3.42%) and for 3.78% subjects, ILI was reported, but a swab was not collected.

Numbers analysed

Efficacy

A total of 11299 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 11257 subjects and included 3776, 3638, and 3843 subjects form the CCI vaccine, IVV and placebo group, respectively.

Immunogenicity

The enrolled immunogenicity population subset consisted of 1049 subjects, of which 240 subjects received CCI vaccine, 747 subjects received IVV and 62 subjects received placebo. The FAS/MITT immunogenicity population subset consisted of 1015 subjects enrolled (235 CCI, 722 IVV; 58 placebo) who actually received a study vaccination, and provided at least one evaluable serum sample both before and/or after baseline. Out of this FAS/MIIT population, 228, 695 and 55 subjects in the CCI vaccine, IVV and placebo groups respectively were included in the PP Population immunogenicity subset. These subjects had correctly received vaccine, provided evaluable serum sample on time, and had no major protocol violation. In the immunogenicity subset, baseline blood samples (day 1) were obtained and analysed for a total of 1044 subjects. Post vaccination blood samples (day 22) were obtained and analysed for a total of 982 subjects: 229, 697, and 56 subjects, respectively.

Outcomes and estimation

Demography and Baseline Characteristics – Enrolled Population

Table 39 Demography and Baseline Characteristics – Enrolled Population

		CCI N=3828	IVV N=3676	Placebo N=3900	All N=11404
Age (Years):		32.7±10.1	33.0±10.2	32.7±10.2	32.8±10.2
Sex:	Male	1740 (45%)	1649 (45%)	1722 (44%)	5111 (45%)
	Female	2088 (55%)	2026 (55%)	2176 (56%)	6290 (55%)
	Not Available	0	1	2	3
Race:	Asian	24 (<1%)	24 (<1%)	24 (<1%)	72 (<1%)
	Black	262 (7%)	247 (7%)	289 (7%)	798 (7%)
	Caucasian	3228 (84%)	3107 (85%)	3301 (85%)	9636 (84%)
	Hispanic	295 (8%)	276 (8%)	272 (7%)	843 (7%)
	Native Amer/Alaska	2 (<1%)	3 (<1%)	5 (<1%)	10 (<1%)
	Pacific/Hawai	6 (<1%)	3 (<1%)	1 (<1%)	10 (<1%)
	Other	11 (<1%)	15 (<1%)	6 (<1%)	32 (<1%)
	Not Available	0	1	2	3
Weight (kg):		76.736±18.542 (N=3826)	76.798±18.492 (N=3672)	76.964±18.576 (N=3896)	76.834±18.536 (N=11394)
Height (cm):		170.99942±9.57120 (N=3826)	171.08669±9.72639 (N=3672)	171.07011±9.76834 (N=3896)	171.05171±9.68822 (N=11394)
Previous Year Vaccination?:	Yes	556 (15%)	511 (14%)	524 (13%)	1591 (14%)
	No	2973 (78%)	2926 (80%)	3101 (80%)	9000 (79%)
	Unknown	299 (8%)	237 (6%)	273 (7%)	809 (7%)
	Not Available	0	2	2	4
Met Entry Criteria:	No	9 (<1%)	12 (<1%)	10 (<1%)	31 (<1%)
	Yes	3819 (100%)	3663 (100%)	3888 (100%)	11370 (100%)
	Not Available	0	1	2	3

Source: Table 14.1.1.3
Categorical parameters: N(%), non-categorical parameters: Mean±SD

The demographic and other baseline characteristics were well matched between the three groups of the enrolled population. The mean age in the three groups was balanced (range, 32.7-33 years). The proportion of males and females in the three groups were similar (ranged 44%-56%). The percentages of subjects with previous vaccination were also balanced among the three groups (range, 13% to 15%). Almost all subjects fulfilled study entry criteria.

Analysis of Efficacy

VE against Vaccine-like strains:

The primary efficacy objective was to estimate the VE of CCI vaccine relative to placebo and IVV relative to placebo for preventing virus-confirmed symptomatic influenza illness caused by vaccine-like virus strains.

CCI Vaccine

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%). 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. 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. See table below.

Table 40 Vaccine Efficacy against culture-confirmed influenza caused by vaccine-like strains:primary objective, per protocol population.

	Proportion of Subjects with Influenza (# Subjects)			VE (%)[1]		Lower Limit of One-Sided 97.5% Simultaneous 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	0.0019 (7/3776)	0.0025 (9/3638)	0.0114 (44/3843)	83.8	78.4	61.0	52.1	0.0005*	0.0035*
A/H3N2	0.0005 (2/3776)	0.0003 (1/3638)	0 (0/3843)	N/E	N/E	N/E	N/E	0.9989	0.9915
A/H1N1	0.0013 (5/3776)	0.0022 (8/3638)	0.0112 (43/3843)	88.2	80.3	67.4	54.7	0.0001*	0.0022*
B	0 (0/3776)	0 (0/3638)	0.0003 (1/3843)	100.0	100.0	-410.0	-429.4	0.3936	0.4002

Similar results were observed for the CCI vaccine group in the MITT population

IVV

The rates of culture-confirmed influenza caused by vaccine-like strains in the per protocol efficacy population were 0.0025 (9/3638) in the IVV group and 0.0114 (44/3843) in the placebo group (VE = **78.4%;** 97.5% CI lower limit: 61%). For the A/H1N1 strain the associated VE and LL of the simultaneous one-side 97.5% CI were **80.3%** and 54.7%, respectively. For strain B, the VE was 100% as no influenza cases were reported in the IVV group while one case was reported in the placebo group. 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. See table below.

Table 41 Vaccine Efficacy against culture-confirmed influenza caused by vaccine-like strains: primary objective, Per Protocol Population

	Proportion of Subjects with Influenza (# Subjects)			VE (%)[1]		Lower Limit of One-Sided 97.5% Simultaneous 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	0.0019 (7/3776)	0.0025 (9/3638)	0.0114 (44/3843)	83.8	78.4	61.0	52.1	0.0005*	0.0035*
A/H3N2	0.0005 (2/3776)	0.0003 (1/3638)	0 (0/3843)	N/E	N/E	N/E	N/E	0.9989	0.9915
A/H1N1	0.0013 (5/3776)	0.0022 (8/3638)	0.0112 (43/3843)	88.2	80.3	67.4	54.7	0.0001*	0.0022*
B	0 (0/3776)	0 (0/3638)	0.0003 (1/3843)	100.0	100.0	-410.0	-429.4	0.3936	0.4002

Similar results were observed for the IVV group in the MITT population

VE against Non-vaccine-like strains:

CCI Vaccine

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.

IVV

The rates of culture-confirmed influenza caused by non-vaccine-like strains in the per protocol efficacy population were 0.0080 (29/3638) in the IVV group and 0.0193 (74/3843) in the placebo group (VE = 58.6%). The lower limit of the simultaneous onesided 97.5% CI for the overall VE of the IVV vs. placebo was 32.9% (p=0.085). Similar results were observed for the IVV group in the MITT population

Table 42 Vaccine Efficacy against culture-confirmed influenza caused by vaccine-like and non-vaccine-like strains-P er Protocol Population

	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	0.0111 (42/3776)	0.0135 (49/3638)	0.0364 (140/3843)	69.5	63.0	55.0	46.7	0.000077*	0.0028*
A/H3N2	0.0016 (6/3776)	0.0033 (12/3638)	0.0065 (25/3843)	75.6	49.3	35.1	-9.0	0.0401	0.53
A/H1N1	0.0016 (6/3776)	0.0027 (10/3638)	0.0148 (57/3843)	89.3	81.5	73.0	60.9	0.000006*	0.00027*
B	0.0079 (30/3776)	0.0074 (27/3638)	0.0159 (61/3843)	49.9	53.2	18.2	22.2	0.37	0.25

[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.
[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.
VE = Vaccine Efficacy = (1 - Relative Risk) x 100%
*p<.025
Source: Table: 14.2.1.3, Table 14.2.1.3.1

Number of Days in Bed, Number of Inpatient and Outpatient Medical visits, and Number of Days of Usual Activity

Among the subset of subjects in the per protocol efficacy population who had culture confirmed influenza and non-missing ILI follow-up data, there was no significant difference between the influenza vaccine groups and placebo in the mean number of days in bed, mean number of inpatient/outpatient visits due to influenza illness, or the mean number of days of usual activity lost due to influenza.

Expanding the number of subjects in the analysis to include all subjects in the per protocol efficacy population, there was a statistically significant difference between CCI and placebo (CCI mean = 0.04 days, n = 3775; placebo mean = 0.12 days, n = 3837, p < 0.0001) in the mean number of days in bed due to culture-confirmed influenza. These significant results largely reflect the difference among the vaccine groups in the rate of culture-confirmed influenza, since subjects in the per protocol population who did not have culture-confirmed influenza were assumed in the analysis to have spent 0 days in bed due to culture-confirmed influenza.

Table 43 Influenza-associated days in bed, number of medical visits and days of usual activity lost, Per protocol Population, subset of Subjects with virus-confirmed-influenza

Variable	Virus -Confirmed Influenza Associated values		
	CCI N=180	IVV N=230	Placebo N=332
Days in bed, mean ± SD	3.9 ± 2.62	2.9 ± 1.98	3.4 ± 2.4
Number of inpatient and outpatient visits and medical consultations	0.8 ± 0.92	0.6 ± 1.0	0.8 ± 1.16
Days of usual activity lost	5.1 ± 3.41	4.0 ± 3.4	4.6 ± 3.45

Source: Table 14.2.1.4

Table 44 Influenza-associated days in bed, number of medical visits and days of usual activity lost, Per protocol Population, All subjects

Variable	Influenza Associated values – All subjects				
	CCI N=3775	IVV N=3638	Placebo N=3837	CCI vs Placebo*	IVV vs Placebo*
Days in bed, mean ± SD	0.04 ± 0.496	0.04 ± 0.404	0.12 ± 0.777	<0.0001**	<0.0001**
Number of inpatient and outpatient visits and medical consultations	0.01 ± 0.138	0.01 ± 0.134	0.03 ± 0.262	<0.0001**	<0.0001**
Days of usual activity lost	0.06 ± 0.635	0.05 ± 0.605	0.16 ± 1.066	<0.0001**	<0.0001**

* Two-sided adjusted p-values from Dunnett's test comparing the CCI least squares (LS) mean to the Placebo LS mean and comparing the IVV LS mean to the Placebo LS mean from an analysis of variance (ANOVA) having factors for vaccine group (CCI, IVV, Placebo) and region (Europe vs USA).
**p<0.001
Source: Table 14.2.1.4

Analysis of Immunogenicity Endpoints

Table 45 Immunogenicity Results HI Assay-Per Protocol Population

	CCI (N=228)						IVV (N=695)						Placebo (N=55)					
Strains	A/H1N1		A/H3N2		B		A/H1N1		A/H3N2		B		A/H1N1		A/H3N2		B	
Prevaccination	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
GMT (95% CI)	34 (27-42)		48 (39-58)		14 (12-16)		35 (31-40)		41 (37-46)		13 (12-14)		37 (24-57)		56 (37-83)		12 (8.89-16)	
Seroprotection rate[b]	110/228	48%	144/228	63%	57/228	25%	369/695	53%	401/695	58%	163/695	23%	33/55	60%	39/55	71%	12/55	22%
95% CI	42-55		57-69		20-31		49-57		54-61		20-27		46-73		57-82		12-35	
Postvaccination (day 22, visit 3)	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Seroconversion rate or significant increase[a]	177/228	78%	135/228	59%	117/228	51%	518/695	75%	470/695	68%	476/695	68%	0/55	0%	0/55	0%	0/55	0%
95% CI	**72-83**		**53-66**		**45-58**		**71-78**		**64-71**		**65-72**		0-6		0-6		0-6	
GMT (95% CI)	566 (483-663)		332 (289-383)		72 (63-84)		499 (455-546)		357 (330-387)		120 (111-131)		36 (26-50)		53 (40-71)		12 (8.81-16)	
GMR (95% CI)or Mean GMT increase	17 (13-21)		6.94 (5.68-8.46)		5.2 (4.31-6.28)		14 (12-16)		8.68 (7.74-9.73)		9.41 (8.45-10)		0.99 (.62-1.56)		0.96 (.64-1.44)		0.99 (.68-1.46)	
Seroprotection rate[b]	226/228	99%	226/228	99%	178/228	78%	682/695	98%	687/695	99%	641/695	92%	33/55	60%	36/55	65%	12/55	22%
95% CI	**97-100**		**98-100**		**72-83**		**97-99**		**98-100**		**90-94**		46-73		51-78		12-35	

Source: Table: 14.2.1.11 (Seroprotection), Table: 14.2.1.12 (Seroconversion or Significant Increase), Table: 14.2.1.13 (GMTs)

[a] CBER criteria for seroprotection (the lower limit of the two-sided 95% CI for the percentage of seroprotected subjects ≥ 70%) and seroconversion (the lower limit of the two-sided 95% CI for the percentage of seroconverted subjects ≥ 40%) rates for each strain for 18-64 year old adults were used in assessing immunogenicity in the age strata under evaluation, [b] Seroprotection is defined as an HI titer ≥ 40; [c] Seroconversion rate is defined as seroconversion (negative pre-vaccination serum [i.e., HI titer <10] and post-vaccination HI titer ≥40) or significant increase (at least a 4-fold increase from non-negative [≥10] pre-vaccination HI titer).

95% CIs in Bold meet respective CBER criteria

The primary measures of immunogenicity, as assessed by HI assay, were: a) percentages of subjects achieving seroconversion at day 22; b) percentages of seroprotected subjects (HI titer ≥40) at day 1 and at day 22; c) geometric mean titers (GMTs) at day 1 and day 22; d) day 22/day 1 geometric mean ratio (GMR).

The percentages of subjects seroprotected or achieving seroconversion were considered statistically compliant with the stated May 2007 CBER Guidance for Industry criteria if:

- the lower limit of the two-sided 95% CI for the percentage of seroprotected subjects (HI antibody titer ≥ 40) at day 22 met or exceeded 70%;
- the lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody titer at day 22 met or exceeded 40%

Auxiliary analyses

Table 46 Summary of Overall Vaccine Efficacy Results Stratified by Region Previous Vaccination, Ethnicity and Sex – Per Protocol Population

		VE(%) (p values)					
		Vaccine-like strains		Non-vaccine-like strains		Vaccine-like and Non-vaccine-like (circulating) strains	
		CCI vs. Placebo	IVV vs. Placebo	CCI vs. Placebo	IVV vs. Placebo	CCI vs. Placebo	IVV vs. Placebo
Region	Europe	88.1 (p=0.0001)*	81.0 (p=0.0015)*	57.8 (p=0.13)	63.3 (p=0.049)	70.1 (p=0.00041)*	70.3 (p=0.00037)*
	USA	-3.8 (p=0.91)	43.0 (p=0.73)	63.4 (p=0.27)	46.3 (p=0.63)	68.3 (p=0.057)	43.0 (p=0.67)
Prior Year Vaccination	Yes	100.0 (p=0.108)	74.3 (p=0.38)	52.4 (p=0.55)	69.1 (p=0.27)	64.9 (p=0.203)	72.9 (p=0.098)
	No	84.0 (p=0.0012)*	81.1 (p=0.0029)*	59.1 (p=0.104)	65.5 (p=0.028)	70.7 (p=0.00017)*	69.4 (p=0.00036)*
Sex:	Female	80.2 (p=0.031)	79.7 (p=0.36)	66.1 (p=0.043)	58.6 (p=0.15)	72.8 (p=0.00062)	63.1 (p=0.0207)
	Male	87.1 (p0.0057)*	77.4 (p=0.038)	44.5 (p=0.64)	58.3 (p=0.29)	64.6 (p=0.038)	62.8 (p=0.0604)
Race	Caucasian	86.1 (p=0.0002)*	78.3 (p=0.0036)*	56.2 (p=0.13)	59.1 (p=0.084)	69.0 (p=0.00013)	63.9 (p=0.0023)
	Non-Caucasian	N/E (p=0.99)	N/E	100.0 (p=0.11)	48.2 (p=0.67)	80.1 (p=0.26)	37.9 (p=0.76)

N/E = Not evaluable
VE = Vaccine Efficacy = (1 - Relative Risk) x 100%; *p<0.025
Source: Table 14.2.1.1, Table 14.2.1.1.1, Table 14.2.1.2, Table 14.2.1.2.1, Table 14.2.1.3, Table 14.2.1.3.1

CCI

Although the interpretation of several of the subgroup analyses was limited by small sample sizes and low event rates, the observed VE of CCI versus placebo against culture confirmed influenza caused by vaccine-like strains was ≥ 80.2% in each of the subgroups examined (region (Europe), prior year vaccination (yes or no), sex (male or female), and race (white)), except for non-whites and subjects from the USA, where circulating strains differed from those in Europe. Only approximately 15% of

subjects were non-white, and among these, none of the placebo subjects and one CCI subject had culture confirmed influenza caused by vaccine-like strains. Likewise, in the

USA, only 2 placebo subjects and 2 CCI subjects had culture confirmed influenza caused by vaccine-like strains. However, sample sizes and event rates were large enough to establish that the VE was statistically different from 40% among whites (p= 0.0002), Europeans (p = 0.0001), males (p= 0.0057), and subjects who did not receive prior year vaccination (p = 0.0012)

As with the subgroup analyses of VE against culture-confirmed influenza caused by vaccine-like strains, the interpretation of results for non-vaccine-like strains was limited by small sample sizes and low event rates within individual subgroups. For the A/H3N2 strain, 8 placebo subjects and no CCI subject had culture-confirmed influenza against non-vaccine-like A/H3N2 (VE = 100%). Likewise, 8 placebo subjects and one CCI subject had culture-confirmed influenza against non-vaccine-like A/H1N1 (VE = 87.3%). Most non-vaccine-like cases of culture-confirmed influenza were caused by the B strain

(29/3776 CCI subjects vs. 59/3843 placebo subjects, VE = 50%). The observed VE of CCI versus placebo against culture-confirmed influenza caused by non-vaccine-like strains was ≥ 52.4% in each of the other subgroups examined (region (Europe or USA), prior year vaccination (yes or no), sex (female), and race (white or nonwhite)) except in males. The observed VE in males was 44.5%.

The observed VE of CCI versus placebo against culture-confirmed influenza caused by vaccine-like and non-vaccine-like strains was ≥ 64.6% in each of the other subgroups examined (region (Europe/USA), prior year vaccination (yes or no), sex (male or female), and race (white or non-white))

The subgroup analysis suggested differences in vaccine efficacy for both CCI vaccine and IVV in subjects from the USA, compared to the efficacy observed in the European subgroup. This might be explained by regional differences in circulating influenza strains. According to the EISS bulletin for 2008, influenza activity in the European Union was predominantly caused by A(H1N1) strains – mainly vaccine-like - for most of the season, and (mostly non-vaccine-like) influenza B had been dominant in Europe from week 9 of 2008 onwards. There was also a low circulation of mainly non-vaccine-like A(H3N2) strains. In contrast, A(H3N2) strains were predominant in the USA for this season according to the CDC 2007-8 influenza season summary, and many did not match the vaccine strain. In addition, the predominant circulating B strains in the US were in most cases dissimilar to the vaccine strain.

2.5.5.3. Summary of main efficacy results

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.

Summary of efficacy for 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 NCT01992094	
Design	Stratified, Randomized, Double-Blind, Multicenter	
	Duration of main phase: Duration of Run-in phase:	day 1 (vaccination) through day 22 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]	
Endpoints and definitions	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.		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	PPS – Per protocol set All subjects in the FAS immunogenicity population who correctly receive the vaccine, have no major protocol deviations leading to exclusion as defined prior to unblinding/analysis, and are not excluded due to other reasons defined prior to unblinding or analysis. Exclusions were considered by objective/time point, ie, sometimes not all data of a subject but only part of the subject's data was removed from the PPS analysis.			
Descriptive statistics and estimate variability	Treatment group	QIVc	TIV1c	TIV2c
	Number of subjects	1250	635	639
	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%-52.6% 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%	

Summary of efficacy results for 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 EudraCT Number: 2015-000133-70 NCT01992107		
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.	
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	PPS – Per protocol set All subjects in the FAS immunogenicity who correctly received the vaccine, had no major protocol deviations leading to exclusion as defined prior to unblinding/analysis, and were not excluded due to other reasons defined prior to unblinding or analysis. Exclusions were considered by objective/time point, ie, sometimes not all data of a subject but only part of the subject's data was removed from the PPS analysis.			
Descriptive statistics and estimate variability	Treatment group	QIVc	TIV1c	TIV2c
	Number of subjects	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 = -6.5%-3.2%	
		Non-inferiority met if the upper limit on the difference seroconversion rates for each strain is <10%		

Summary of efficacy for V130_12

Title: A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥2 years to <18 Years of Age

Study identifier	Protocol V130_12 EudraCT 2016-002883-15 NCT 03165617	
Design	Stratified, Randomized, Observer-blind, Comparator Controlled, Multicenter Study	
	Duration of main phase:	Day 1 through Day 180/209* or end of influenza season, whichever is longer * depending upon previous vaccination status
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority (Absolute Vaccine Efficacy)	
Treatments groups	QIVc: cell-derived quadrivalent influenza vaccine	Season 1 [Southern Hemisphere 2017]: Strain Type A/Singapore/GP1908/2015 IVR-180 (H1N1) Strain Type A/HongKong/4801/2014 (H3N2) Strain Type B/Utah/9/2014 (B Yamagata) Strain Type B/HongKong/259/2010 (B Victoria) Season 2 [Northern Hemisphere 2017-2018]: Strain Type A/Singapore/GP1908/2015 IVR-180 (H1N1) Strain Type A/Singapore/GP2050/2015 (H3N2) Strain Type B/Utah/9/2014 (B Yamagata) Strain Type B/HongKong/259/2010 (B Victoria) Season 3 [Northern Hemisphere 2018-2019]: Strain Type A/Singapore/GP1908/2015 IVR-180 (H1N1) Strain Type A/North Carolina 04/2016 (H3N2) Strain Type B/Singapore/INFTT-16-06 10/2016 (B Yamagata) Strain Type B/Iowa/06/2017 (B Victoria) 1 or 2 doses depending upon previous vaccination status and/or age
	Comparator: Non-Influenza vaccine	Meningococcal(Groups A,C,Y,W-135)conjugate vaccine (Menveo) 1 dose plus placebo (0.9% w/v saline for injection) if needed for blinding purposes

Endpoints and definitions	Co-Primary endpoints	Absolute Vaccine efficacy	Time from last study vaccination to the onset of the first occurrence of RT-PCR- or culture-confirmed influenza, due to any influenza Type A or B strain, and regardless of an antigenic match to the strains selected for the seasonal vaccine that occurred more than 14 days after the last vaccination until the end of the influenza season. The primary and co-primary endpoints were met if the lower limit of the 2-sided 95% CI of the absolute vaccine efficacy estimate was greater than 20% (primary endpoint) using protocol definition of ILI in 2 to <18 yrs or greater than 30% (co-primary endpoint) in subjects 3 to <18 yrs of age
Database lock	01 Oct 2019		

Results and Analysis

Analysis description	**Primary Analysis (Efficacy)**		
Analysis population and time point description	• FAS-Efficacy = All subjects in the All-Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination. • Day 14 to Day 180 or until the end of the influenza season, whichever is longer		
Descriptive statistics and estimate variability	**Treatment group**	**QIVc**	**Comparator**
≥2 years to <18 years	Number of subjects (FAS-Efficacy Set, (≥2 years to <18 years)	2257	2252
	RT-PCR or Culture Confirmed due to Any Strain, Number of cases (attack rate %)	175 (7.8%)	364 (16.2%)
≥3 years to <18 years	Number of subject (FAS-Efficacy Set, (≥3 years to <18 years)	2208	2201
	RT-PCR or Culture Confirmed due to Any Strain , Number of cases (attack rate %)	171 (7.7%)	351 (15.9%)

Effect estimates per comparison	**Primary endpoint** (≥2 to <18 yrs)	**Comparison groups**	**QIVc to Comparator**
		Vaccine Efficacy (%): 1 - hazard ratio (QIVc- vs. Comparator) Cox proportional hazard model	54.63%
		2-sided 95% Confidence interval	(45.67%, 62.12%)
	Success criteria for the primary efficacy endpoint was met if the LL of the 2-sided 95% CI of the VE estimate was greater than 20% (primary endpoint) using the protocol definition of ILI for the entire age range (2 to <18 years of age).		
	Co-Primary endpoint (≥3 to <18 yrs)	**Comparison groups**	**QIVc to Comparator**
		Vaccine Efficacy (%): 1 - hazard ratio (QIVc- vs. Comparator) Cox proportional hazard model	54.03%
		2-sided 95% Confidence interval Cox proportional hazard model	(44.80%, 61.71%)

	The co-primary efficacy objective was to be assessed on condition that the primary efficacy objective was successfully demonstrated. The success criterion used for this co-primary objective was as follows: The efficacy of the QIVc was demonstrated if the LL of the 2-sided 95% CI for VE was above 30%.

Summary of efficacy for V130_10

Title: A Phase 3, Randomized, Observer-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) and a United States-licensed Quadrivalent Influenza Virus Vaccine (QIV) in Healthy Subjects 6 Months Through 47 Months			
Study identifier	V130_10 NCT04074928 2020-002785-13		
Design	Randomised, Double blind, Multicenter		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Day 1 (vaccination) through day 29/57 not applicable not applicable	
Hypothesis	Non-inferiority		
Treatments groups	QIVc	A/Idaho/07/2018 (A/H1N1) A/Indiana/08/2018 (A/H3N2) B/Singapore/INFTT-16-0610/2016 (B/Yamagata) B/Iowa/06/2017 (B/Victoria)	
	US-licensed QIV	A/Brisbane/02/2018 (IVR-190) (A/H1N1) A/Kansas/14/2017 (X-327) (A/H3N2) B/Phuket/3073/2013 (B/Yamagata) B/Maryland/15/2016 (B/Victoria)	
Endpoints and definitions	Primary endpoint n°1	Geometric mean titre (GMT) ratios for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV	
	Primary endpoint n°2	Seroconversion rate (SCR) differences for each vaccine strain in subjects 6 months through 47 months of age receiving QIVc or the US-licensed QIV	
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	PPS – Per protocol set Per Protocol Set (PPS): All subjects in the FAS who received vaccine on Day 1, provided serology specimens which yielded valid serology assay results from both Day 1 and Day 29 (previously vaccinated subjects) or Day 1 and Day 57 (not previously vaccinated subjects) and for whom there was no protocol deviation that was medically assessed as having potential to impact the immunogenicity results. End point timeframe: 28 days after last vaccination (Day 29 in previously vaccinated subjects, Day 57 in not previously vaccinated subjects)		
Descriptive statistics and estimate variability	Treatment group	QIVc	US-licensed QIV
	Number of subjects	1092	575
	GMT (Day 29/57)	A/H1N1 = 78 A/H3N2 = 23.1 B/Yamagata = 35.6 B/Victoria = 22.4	A/H1N1 = 57.3 A/H3N2 = 23.9 B/Yamagata = 26.0 B/Victoria = 19.6

	2-sided 95%CI	A/H1N1 = 70.75 - 86.03 A/H3N2 = 21.21- 25.12 B/Yamagata = 32.93- 38.58 B/Victoria = 20.70- 24.19	A/H1N1 = 50.76 - 64.63 A/H3N2 = 21.57 - 26.57 B1 = 23.54- 28.63 B2 = 17.81 - 21.58
	Seroconversion (Day 29/57)	A/H1N1 = 58.24% A/H3N2 = 27.64% B/Yamagata = 46.52% B/Victoria = 30.31%	A/H1N1 = 46.78% A/H3N2 = 30.77% B/Yamagata = 31.65% B/Victoria = 24.35%
	95%CI	A/H1N1 = 55.25%- 61.19% A/H3N2 =(-24.99%- 30.42% B/Yamagata = 43.53% - 49.53% B/Victoria = 27.60%- 33.13%	A/H1N1 = 42.64,%- 50.96% A/H3N2 = 27.01% - 34.73% B1 = 27.87%- 35.63% B2 = 20.89%- 28.07%
Effect estimate per comparison	**Primary endpoint n°1**	Comparison groups	Vaccine group ratio ($GMT_{US\ Licensed\ QIV}/GMT_{QIVc}$)
		GMT	A/H1N1 = 0.73 A/H3N2 = 1.04 B/Yamagata = 0.73 B/Victoria = 0.88
		95%CI	A/H1N1 = 0.645-**0.836** A/H3N2 = 0.927–**1.160** B/Yamagata = 0.656-**0.809** B/Victoria = 0.791-**0.972**
		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 US Licensed QIV – seroconversion rate QIVc.)
		Seroconversion rate	A/H1N1 = -11.46% A/H3N2 = 3.13% B/Yamagata = -14.87% B/Victora = -5.96%
		95%CI	A/H1N1 = -16.447%- **-6.423%** A/H3N2 = -1.443% - **7.812%** B/Yamagata = -19.610%,-**9.983**% B/Victora = -10.327%,-**1.440**%
		Non-inferiority met if the upper limit on the difference seroconversion rates for each strain is <10%	

Summary of efficacy for V58P13

Title: A Phase III, Randomized, Observer-Blind, Placebo-Controlled, Multicenter Study to Assess Clinical Efficacy of a Cell-Derived Subunit Influenza Vaccine and an Egg-Derived Subunit Influenza Vaccine in the 2007-2008 Influenza Season in Healthy Adult Subjects		
Study identifier	V58P13 EudraCT number 2007-002871-15 NCT00630331	
Design	Observer-Blind, Placebo-Controlled, Multicenter Study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months not applicable not applicable
Hypothesis	Superiority (Absolute Vaccine Efficacy)	
Treatments groups	TIVc (Flucelvax/Optaflu)	A/Solomon Islands/3/2006 (H1N1)-like A/Wisconsin/67/2005 (H3N2)-like B/Malaysia/2506/2004-like
	TIVeA (IIV) (Agrippal)	A/Solomon Islands/3/2006 (H1N1)-like A/Wisconsin/67/2005 (H3N2)-like B/Malaysia/2506/2004-like
	Placebo	No active component

Endpoints and definitions	Co-Primary endpoints	Absolute Vaccine efficacy	Number of Subjects With Culture-Confirmed Influenza Illness Caused by Vaccine-like Strains. The vaccine efficacy of TIVc and IVV vaccines was estimated relative to Placebo group as the number of subjects prevented against virus-confirmed symptomatic influenza illness caused by each of three vaccine-like virus strains.

Results and Analysis

Analysis description	**Primary Analysis (Efficacy)**			
Analysis population and time point description	Per protocol (PP) efficacy population i.e. the subjects in the exposed efficacy population who correctly received the vaccine and provided evaluable swab samples at the relevant time points.			
Descriptive statistics and estimate variability	**Treatment group**	**CCI Vaccine**	**IVV Vaccine**	**Placebo**
		3776	3638	3843
	Number of Subjects With Culture-Confirmed Influenza Illness Caused by Vaccine-like Strains			
	Overall	7	9	44
	A/Wisconsin/67/2005 (H3N2)-like	2	1	0
	A/Solomon Islands/3/2006 (H1N1)-like	5	8	43
	B/Malaysia/2506/2004-like	0	0	1

Effect estimates per comparison	**Primary endpoint**	**Comparison groups**	CCI vaccine vs. Placebo	TIV vaccine vs. Placebo
	Overall	Vaccine efficacy (VE)	83.8%	78.4%
		Lower Limit of One-Sided 97.5% Simultaneous CI of VE	61%	52.1%
		P-value	0.0005*	0.0035*
	(A/H3N2)	Vaccine efficacy (VE)	NE	NE
		Lower Limit of One-Sided 97.5% Simultaneous CI of VE	NE	NE
		P-value	0.9989	0.9915
	(A/H1N1)	Vaccine efficacy (VE)	88.2%	80.3%
		Lower Limit of One-Sided 97.5% Simultaneous CI of VE	67.4%	54.7%
		P-value	0.0001*	0.0022*

	B	Vaccine efficacy (VE) of CCI vaccine vs. Placebo (B)	100%	100%
		Lower Limit of One-Sided 97.5% Simultaneous CI of VE	-410%	-429.4%
		P-value	0.3936	0.4002
	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. 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 < 0.025, then the comparison is statistically significant. VE = Vaccine Efficacy = (1 - Relative Risk) x 100 % N/E = Not Evaluable *p <0.025			

2.5.5.4. Clinical studies in special populations

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 compared to QIVc.

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

In addition, there are three studies that exclusively enrolled paediatric subjects (V130_03, V130_12, V130_10, V58P12) during QIVc development, and three (V58P12, V58P16, V58P15, V58_31) during TIVc development.

2.5.5.5. Supportive studies.

The QIVc clinical development program was supported by studies with TIVc, which were assessed during the MAA and post-authorisation procedures of Optaflu.

- One phase II/III immunogenicity study comparing TIVc to a TIV produced in embryonated eggs in children (V58P12), assessed as a FUM in the context of Optaflu (TIVc).

- Other studies of limited relevance for the current procedure: Nine TIVc studies to evaluate safety and immunogenicity in adults (V58P1, V58P2, V58P4, V58P4E1, V58P4E2, V58P5, V58P9, V58-23, V58_30OB) and four TIVc studies in children/adolescents (V58P12, V58P15, V58-31, V58P16).

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

	Day 22/Day 50	V58P12 Subjects 4 to < 9 Years Not Previously vaccinated (Cohort 3)		V58P12 Subjects 9 to < 18 Years (Cohort 1)	
		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 = hemagglutination 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 48 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 48 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 the following Table, 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 49 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	446	505	749	833

(95%CI)	(355; 561)	(403; 631)	(649; 866)	(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 50 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 51 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		N = 260	N = 260	N = 29	N = 11
	Day 1 Prevaccination (95% CI)	5 (5-5)	5 (5-5)	5 (5-5)	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		N = 70	N = 54	N = 9	N=5
	Day 1 Prevaccination (95% CI)	5 (5-5)	5 (5-5)	5 (5-5)	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		N = 370	N = 346	N = 88	N = 88
	Day 1 Prevaccination (95% CI)	5 (5-5)	5 (5-5)	5 (5-5)	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

2.5.6. Discussion on clinical efficacy

The claimed indication for Flucelvax is prophylaxis of influenza in adults and children from 2 years of age.

In support of this submission, and in line with the EMA/ETF recommendations, no new clinical studies were submitted for Flucelvax (TIVc).

The efficacy assessment of Flucelvax (TIVc) is mainly based in the data generated during development of Flucelvax tetra (QIVc); specifically during the iMAA (EMEA/H/C/004814) and during the extension of indication variation (EMEA/H/C/004814/II/0013). This comprises four studies. These, together with the Optaflu (TIVc) efficacy study, are considered pivotal:

- Two phase III immunogenicity studies comparing QIVc and TIVc in adults (V130_01) and children 4 to 18 years of age (V130_03), assessed as part of the initial MAA of Flucelvax Tetra (QIVc), supporting the initial indication from 9 years of age.
- One phase III/IV efficacy and immunogenicity study in children 2 to 18 years of age (V130_12), assessed as a variation of Flucelvax Tetra (QIVc), supporting an extension of indication in children from 2 years of age.
- One phase III immunogenicity study in children 6 to 47 months of age (V130_10), assessed as a post-authorization measure to Flucelvax Tetra (QIVc)
- One phase III immunogenicity and efficacy study in adults (V58P13), assessed as a FUM in the context of Optaflu (TIVc).

There are other studies carried out during the development of Optaflu (TIVc), whose relevance is limited and are only considered supportive in the context of this MAA.

- One phase II/III immunogenicity study comparing TIVc to a TIV produced in embryonated eggs in children (V58P12).
- One phase I/II dose-finding study in children 6-48 months of age that did not result in any dose selection (V58P16) (not considered relevant in terms of efficacy for the current application).
- Nine TIVc studies to evaluate safety and immunogenicity in adults (V58P1, V58P2, V58P4, V58P4E1, V58P4E2, V58P5, V58P9, V58-23, V58_30OB) and two TIVc studies in children/adolescents (V58P15, V58-31).

Studies V130_03, V130_01, V58P13, V58P12

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 stratified analysis of vaccine effectiveness 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 adult 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 $\geqslant$1:10) at baseline. Thus,

the vaccine induces an adequate immune response in both age groups independently on the serostatus at baseline. Since the comparator vaccine (TIVc) was not approved in children in the EU, and since the non-inferiority of the TIVc compared to an egg-based vaccine (TIVe) has not been demonstrated in children 4-8 years of age, the indirect immunobridging was considered an uncertainty in the 4-9 years old and, therefore, at the time of initial assessment QIV was approved in children from 9 years of age.

The applicant 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 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 were performed in the clinical efficacy study V130_12 (subjects 2 to < 18 years of age), and in the two QIVc immunogenicity and efficacy studies V130_10 and V130_14 (not submitted in this application) 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.

Overall study V130_01 demonstrated a robust immune response for the QIVc vaccine in adults.

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 49 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.Overall, study V58P13 demonstrated absolute efficacy of TIVc vaccine to prevent influenza as well as robust immunogenicity profile in adults 18-49 years old.

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, 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.

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 could be given at the same time as other vaccines. However, it is considered that there are not data to support the current statement in 4.5 regarding coadministration with other vaccines for Flucelvax. Therefore, the applicant has committed to submit a type II variation to submit data and to update section 4.5 of the SmPC.

Study V130_12

Design and conduct of clinical studies

In general, the design of the phase III/IV study conducted to evaluate clinical efficacy, safety and immunogenicity of the QIVc in children 2 to < 18 years of age (V130_12 clinical study) is considered adequate.

This absolute efficacy study was a regulatory (post-marketing) requirement to confirm the clinical benefit of QIVc for use in children ≥4 years of age in the US. To fulfil additional registration requirements with the European Union (EU) children ≥2 years of age were also enrolled in this study to further evaluate QIVc in a broader age range.

Regarding the design of the trial, the guideline on Influenza vaccines specifically requires a demonstration of vaccine efficacy in the 6-36 month group, for an indication that includes children of this age. For children older than 36 months, the Guideline states: "For an indication for use in children aged from 3 years up to approximately 9 years, in whom the proportion that is primed is likely to be very variable in different settings, authorization should usually be based on demonstrating that the immune responses to the selected dose and regimen are at least as good as those observed in children aged 6-36 months in whom efficacy has been satisfactorily demonstrated." For this age group (3 to 9 YOA) it also states: "In cases where vaccine efficacy could not be demonstrated in the 6-36 month old, the possible basis for an authorisation for use in 3-9 year olds should be discussed with competent regulatory authorities." In line with this recommendation, the applicant discussed the design of V130_12 study in a follow-up scientific advice in 2016 (EMEA/H/SA/2628/2/FU/1/2016/PED/II) and the CHMP agreed that this study was carried out to demonstrate clinical efficacy in children older than 3 years of age. Originally study V130_12 was designed to be performed in children 4 to 18 YOA, but in a protocol amendment the lower age was changed to 2 YOA. Therefore, the applicant submitted clinical efficacy data in the whole 2 to <18 age group, which was acknowledged and welcomed, and in accordance with CHMP scientific advice. The results for the 3 to 18 years group clearly support the indication for this age group. However, as it was commented above, a small number of children (49 subjects) in the 24-36 months of age received QIVc in study V130_12 so that the indication from 24 to 36 months of age was questioned. The applicant explained that despite the relatively small number of study participants aged 2 to <3 years, the incidence of any RT-PCR- or culture-confirmed influenza, reported during the study period, was high: 13/51 subjects (25.5%) in the comparator group, and 4/49 subjects (8.2%) in the QIVc group. The applicant also highlighted that the estimate of vaccine efficacy in children in the 2 to <3 years of age group was 67.97 (95% CI: 8.00, 88.79) and was consistent with efficacy estimates in other age groups, and in the overall study population. In addition, the Company mentioned that the efficacy of QIVc in "previously vaccinated" and "not previously vaccinated" children was comparable and that there was no difference in strain-specific efficacy against the different influenza strains between these two groups of influenza vaccinated subjects. This point is considered important, since the youngest children are mostly influenza-naïve and it is a potential concern that they do not respond to influenza vaccines as well as older children. These data supported the indication in children aged 2 to <3 years.

The study was carried out as observer blind. Although the optimal design would have been a double blinded trial, it is considered that the observer blind strategy used here is sufficient because we consider very unlikely that this design would have affected the study outcomes. Subjects were randomized in a 1:1 ratio to QIVc or non-influenza comparator vaccine, Menveo (GSK Biologicals S.A.), a Neisseria meningitidis serogroup A, C, W-135, Y conjugate vaccine. The randomization was stratified by age (2 to < 9 years and 9 to < 18 years). Subjects between 2 to < 9 years of age were further stratified by previous influenza vaccine status. Study subjects were scheduled to receive either a single dose of 0.5 mL of the study vaccine or a two-dose study vaccination regimen separated by approximately 4 weeks

as clinically indicated depending on age and previous influenza vaccination history. This scheme is in accordance with paediatric influenza vaccine dosing recommendations and consistent with international recommendations.

The baseline characteristics of the enrolled subjects were well balanced between treatment groups, and there were a small percentage of subjects withdrawn from the study. The percentages and reason for discontinuation were similar in the two treatment groups, and there was no indication of selective discontinuation. Although in the overall population of this trial, the races and ethnic origins were all well balanced and represented, in the group of the 2 to < 9 years only white children and mostly Not Hispanic or Latino were recruited. On the other hand, there are only 100 subjects in the group 2 to 3 years (49 received QIVc and 51 the comparator vaccine), and this is considered a bit scarce.

The definition and use of the PPS (Per Protocol Population Immunogenicity Set) population for immunogenicity comparisons is also considered adequate.

As commented above there were some issues regarding to the loss of capacity of the A/H3N2 influenza virus strains to agglutinate chicken or turkey erythrocytes. To solve this situation, the applicant used the MN assay (an exploratory objective) to measure the serologic response against the A/H3N2 strain contained in QIVc in Seasons 2 and 3, and this approach was found satisfactory.

The primary objective of V130_12 to demonstrate the absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain in subjects who were 2 years to < 18 years of age was met.

No other measurements now cited in EMA/CHMP/VWP/457259/2014 (for example, single radial hemolysis, cell-mediated immunity, antigen-specific T-cell frequencies, CD4+ and CD8+ responses, activation of memory B cells, or evaluation of anti-neuraminidase antibodies) were assesed in the V130_12 protocol.

Based on all these considerations, the design of the clinical trial is considered appropriate.

Efficacy data and additional analyses

The primary and co-primary efficacy endpoints, absolute VE (aVE) relative to comparator against any influenza Type A or B strain were achieved. The analysis showed that QIVc prevented RT-PCR- or culture confirmed influenza caused by any Type A or B strain in subjects 2 to < 18 years of age (primary efficacy endpoint) and 3 to < 18 years of age (co-primary endpoint). The VE of QIVc in children 2 to < 18 years of age was 54.6% (95% CI: 45.7 to 62.1). Success criteria were met as the LL of the 2-sided 95% CI was above 20%. The VE of QIVc in children 3 to < 18 years of age was 54.0% (95% CI: 44.8 to 61.7). The success criterion was met as the LL of 2-sided 95% CI for VE is above 30%.

Moreover, the secondary efficacy objectives, that were efficacy against RT-PCR or culture-confirmed influenza in the overall study population 2 to < 18 years of age either due to any influenza type A or B strain or due to influenza type A or B antigenically matched strains were also met. The VE numbers were 54.63% (95% CI [45.67, 62.12]) for PCR-confirmed regardless of antigenic match, 60.81% (95% CI [51.30, 68.46]) for cultured-confirmed regardless of antigenic match, and 63.64% (95% CI [53.64; 71.48]) for culture-confirmed and matched to the strains contained in the vaccine. Also, although in some cases the LL of the 95% CI was barely below 20%, when looking at specific strains the success criterion was also met.

Moreover, aVE analyses was also performed in different subgroups: by age, by vaccination status, by race, by sex, by country or region, and by season/year treated. As discussed below, none of these analyses questioned the superior aVE of the vaccine vs the comparator.

As it can be seen in the following summary table, the aVE (RT-PCR or Culture confirmed, any strain) was also analysed in two other age cohorts (different from the 2 to < 18 or 3 to < 18 for the primary and coprimary efficacy endpoints). The aVE observed were similar between in the two cases.

The aVE for matched strain was again, similar between all the subgroups, although in the 2 to < 4 group the aVE was a bit higher. Interestingly, the unmatched aVE seems to be similar between all the subgroups but the 2 to 4 years old group. This could mean that this vaccine cannot provide cross protection against non-matching circulating strains to this age strata, although this cannot be concluded due to the low number of subjects in this age strata.

Age group (years)/aVE	2 to < 4	4 to < 18	2 to < 9	9 to < 18	2 to < 18 (whole study)	3 to < 18
Overall RT-PCR or culture confirmed (95%CI)	62.66 (38.06,77.49)	53.33 (43.38, 61.54)	50.51 (38.72, 60.22)	61.85 (47.37, 72.34)	54.63 (45.67, 62.12)	54.03 (44.80,61.71)
Cultured confirmed **Matched** strain	77.08 (52.27, 89.00)	61.58 (50.25, 70.33)	63.04 (50.66,72.32)	64.78 (44.84,77.51)	63.64 (53.64, 71.48)	62.30 (51.81,70.51)
Cultured confirmed **Unmatched** strain	-5.14 (-247.52,68.19)	46.73 (8.21, 69.09)	42.86 (-7.89, 69.74)	41.75 (-27.21,73.33)	42.47 (5.81,64.86)	44.52 (8.58, 66.33)

As it is detailed in section on "Demographic and Baseline data", 50.7% of the subjects were in the age strata 2 to<9YOA, so the high aVE obtained in this age subgroup supports the requested indication for this age subgroup.

Regarding to the vaccination status, in subjects 2 to <18 years of age, the VE of QIVc compared with comparator vaccine for any RT-PCR- or culture-confirmed strain tended to be higher in subjects "previously vaccinated" against influenza 58.67 (47.45, 67.50) as compared to "not previously vaccinated" subjects 48.39 (32.13; 60.75]. Overall, there were 314 RT-PCR- or culture-confirmed (178 Type A and 136 Type B) cases in "previously vaccinated" compared to 225 (132 Type A and 95 Type B) in "not previously vaccinated" subjects. As it can be seen in the following table, there was no difference between "previously vaccinated" and "not previously vaccinated" subjects in strain specific VE.

VE (95%CI)	**Overall RT-PCR or culture confirmed**	**Type A/H1N1**	**Type A/H3N2**	**Type B**
Previously vaccinated	58.6 (47.45,67.50)	86.8 (72.34, 93.70)	42.65 (13.5, 61.97)	51.90 (31.25, 66.35)

Not previously vacci	48.39 (32.13, 60.75)	73.23 (50.50, 85.52)	41.30 (2.61,64.61)	40.97 (10.62, 61.01)

The analysis showed that VE was similar for White subjects 54.74 (41.54, 64.96) and for Asian subjects 53.70 (40.24,64.13). There were too few subjects amongst the other racial groups to estimate vaccine efficacy. As expected, the VE was also similar for male subjects 54.70 (42.04,64.59) and female subjects 54.47 (40.64,65.08).

Finally, the analysis showed that VE varied across countries and was highest in Australia (VE: 93.70% [95% CI: 52.28; 99.17]). In 5 out of the 7 countries, for which the assessment could be made, QIVc showed a statistically significant decrease in RT-PCR- or culture-confirmed influenza in subjects 2 to <18 years of age, in 2 countries the VE was not statistically significant, Thailand (VE: 23.85% [95% CI: -53.10; 62.13]) and Finland (VE: 38.30% [95% CI: -2.78; 62.96]). Overall, for every country the VE against Type A was higher than against Type B. The VE against Type A was driven by the VE against Type A/H1N1 strains.

All the data and analysis are considered adequate.

Immunogenicity data

The secondary immunogenicity objective was to characterize the immunogenicity of QIVc by hemagglutination inhibition (HI assay) 3 weeks after the last vaccination in a subset of 751 subjects 2 to <9 years of age, who were enrolled in Season 2 (n=432) and Season 3 (n=319). From those, 721 (n=422 [Season 2]; n=299 [Season 3]) were included in the FAS Immunogenicity.

Immunogenicity were assessed at baseline (Day 1; all subjects in immunogenicity subset), at Day 22 (all "previously vaccinated" subjects receiving a single dose of the study vaccine), and at Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all4 influenza strains using the HI assay.

The immunogenicity objectives were evaluated using the immunogenicity subset of subjects. The analysis was based on the FAS Immunogenicity. The Immunogenicity data was analysed descriptively and no success criteria were applied.

As already commented above, the HI results were inconsistent in Season 2 for the A/H3N2 strain. To solve this situation, the applicant has used the MN assay (an exploratory objective) to measure the serologic response against the A/H3N2 strain contained in QIVc. This solution is agreeable.

The data from trial V130_12 showed that children from 2 to <9 years (seronegative at baseline) had developed in general an immune response after vaccination with QIVc against all strains. Although, post-vaccination GMTs were lowest against the B strains, but higher for B-Yamagata compared with B-Victoria. Similar results were observed for subjects seropositive (HI titres ≥1:10) at baseline. Specifically, baseline QIVc GMTs assessed by either HI or MN were higher in subjects whose parents/LAR reported prior vaccination and QIVc GMRs were higher in subjects who were not previously vaccinated. Also, post-vaccination GMTs were lowest against the B strains, but higher for B-Yamagata compared with B-Victoria. Overall, this is the situation observed with influenza vaccines. Thus, it can be considered that the vaccine induces an adequate immune response in children 2 to <9 years independently on the serostatus at baseline.

The vaccine strain composition changed between seasons. Except for the Type A/H1N1 vaccine strain, all other vaccine strains (Type A/H3N2, Type B/Yamagata and Type B/Victoria) were updated for each

season. Therefore, all the immunogenicity results were presented by season, even in the case where the strain did not change (eg, A/H1N1). The FAS Immunogenicity was predominantly White (99.0%), which is a markedly higher proportion than in the All Enrolled Set. The applicant explained that this was due to the geographical location of these subjects (Estonia, Finland, Poland, and Lithuania) limited by enrolment in Seasons 2 and 3. Four subjects were of Hispanic or Latino origin, all other subjects were of "Not Hispanic or Latino" origin. It would have been optimal to include participants from different ethnic groups, however having in mind all the scientific knowledge on the immune response to influenza vaccines in different races, it is not expected that this issue introduces any bias.

In conclusion, there was a robust and substantial immune response across the 2 seasons in subjects who received QIVc; even with seasonal differences in vaccine strains and baseline GMTs.

Study V130_10

Study V130_10 was undertaken to expand the age indication and support licensure of QIVc for use in children 6 months of age and older in the US (from the currently approved indication of 4 years and older) and to further support regulatory submissions in other regions as required.

Study (V130_10) has been submitted in this application and was also part of an EU Paediatric Investigation Plan (PIP) for Flucelvax Tetra. The agreed PIP included also study V130_14, requested by EMA,: Study V130_14 – A Phase 3 efficacy, immunogenicity, and safety study of QIVc compared with a non-influenza comparator in healthy children 6 months through 47 months of age. Study V130_14 was requested by CHMP in line with the Guideline on Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1), that states that in order to grant an indication in children 6 to 36 months of age, efficacy data should be submitted by the applicant. In this sense, the immunogenicity data from study V130_10, do not trigger any regulatory action in the EU.

Study V130_10 was a Phase 3, randomized, observer-blind, comparator-controlled, multicenter, noninferiority study designed to evaluate the immunogenicity and safety of QIVc compared with a US-licensed QIV in children 6 months through 47 months of age. QIVc (Flucelvax Tetra in Europe and Flucelvax Quadrivalent in the US) is a cell-based quadrivalent inactivated subunit influenza vaccine prepared from virus propagated in Madin-Darby Canine Kidney (MDCK) cells. The US-licensed QIV (Afluria Quadrivalent) comparator vaccine is an egg-based inactivated influenza vaccine. The comparator US-licensed vaccine is Afluria Quadrivalent, which is not authorised in the EU.

The conclusions that are obtained from the submitted V130_10 study are the following:

- The predefined success criteria for the 8 co-primary immunogenicity endpoints were met, thus demonstrating a noninferior immune response for QIVc compared with the US-licensed QIV in children 6 months through 47 months of age.
- The secondary and exploratory immunogenicity objectives of the study described humoral immunogenicity of QIVc and the US-licensed QIV based on HAI and MN assay data, using cell- and egg-derived target viruses. For assays using cell-derived target viruses, the QIVc response was similar to the US-licensed QIV response for the A/H3N2 and B/Victoria strains whereas for the A/H1N1 and B/Yamagata strains, the QIVc response was observed to be higher. For assays using egg-derived target viruses, there were no notable differences between the 2 vaccines for all 4 strains. Overall, the evaluation of immunogenicity for the secondary objectives reinforces the finding that the immune response to QIVc is noninferior to the immune response to the US-licensed QIV.
- The exploratory CMI evaluation showed T-cell responses to both vaccines at expression levels not unexpected for inactivated, non-adjuvanted vaccines.

- QIVc and the US-licensed QIV were well tolerated in this population of children 6 months through 47 months of age. The 2 vaccines had a similar and clinically acceptable safety profile. No safety concerns were identified in the study.

The MAH is not proposing changes in the Product Information (PI) as a consequence of this study and this is agreed. It is considered that no update of the PI is warranted as study requested V130_14 in the same age population will render the efficacy, immunogenicity and safety results necessary for the assessment of the indication from 6 months of age in the EU.

In summary, to support the new marketing authorisation for Flucelvax trivalent formulation (TIVc) clinical relevant studies previously submitted and reviewed as part of previous filings with EMA were submitted for this application.

The efficacy of the previously authorized TIVc was established for adults in study V58P13, and inferred by immunobridging to an egg-based vaccine in children from 3 years of age in study V58P12. The efficacy of QIVc was established for children from 2 years of age in study V130_12 and was inferred by immunobridging to TIVc in adults (study V130_01) and children from 4 years of age (study V130_03).

Therefore, the data for the QIVc is relevant for the updated TIVc, as the TIVc strain composition is identical to QIVc (except for omission of the B strain Yamagata lineage, which should not have any impact on the immunogenicity and efficacy) and supports the indication of Flucelvax TIVc in prevention of influenza in adults and children from 2 years of age.

2.5.7. Conclusions on the clinical efficacy

The CHMP concludes that clinical efficacy/immunogenicity data supports an indication in adults and children from 2 years of age.

2.5.8. Clinical safety

The key safety outcomes to support licensure of TIVc in people aged 2 years and older are provided in Table below.

Table 52: Key Safety Outcomes

Source	Studies Summarized	Key Safety Outcomes
QIVc initial m2.5	TIVc studies QIVc studies V130_01 and V130_03	The TIVc studies confirmed the following: • TIVc is well tolerated in all age groups, based on a safety database of over 5000 subjects exposed to TIVc in clinical trials and postmarketing experience in more than 10 million individuals. The QIVc clinical studies confirmed the following:

Source	Studies Summarized	Key Safety Outcomes
		• QIVc is well tolerated in all age groups, based on a safety database of: >1150 adult subjects including elderly (≥ 18 years of age) and > 1150 pediatric subjects (4 to < 18 years of age) exposed to QIVc, as well as > 5000 subjects exposed to TIVc. • The reactogenicity profile of QIVc was similar to that reported for TIVc. • There was no noticeable difference in percentages of subjects reporting unsolicited AEs between the QIVc and TIVc comparator groups. Both SAEs and NOCDs occurred in a low percentage of subjects. • Overall, no specific safety signals were identified that could potentially affect this benefit risk assessment of the QIVc vaccine. • Analyses of safety and reactogenicity by subgroups such as age, sex, and racial/ethnic origin did not reveal any meaningful differences between the QIVc and TIV comparator groups.
QIVc m2.5 addendum 1	QIVc study V130_12	The safety of QIVc in the pediatric population has been demonstrated now in two clinical studies in which 3417 children less than 18 years of age received the vaccine. In study V130_12, subjects received QIVc or a non-influenza comparator, Men ACWY and overall the rates of solicited and unsolicited adverse events were similar. The majority of subjects did not report any local or solicited adverse event, and the most commonly reported local reactions were pain and tenderness and systemic were headache and fatigue. Fever was reported by approximately 5% of subjects and severe fever was rare (< 1%). The majority of solicited AE were mild or moderate in severity and resolved within 3 or 4 days after onset. In study V130_12, among subjects in the QIVc group, there were 2 reports of not related mild febrile convulsion. No safety concern or risk was identified after administration of the second vaccine during the QIVc studies. No related serious adverse event was reported during Study V130_12. The safety profile of QIVc in study V130_12 was similar to that reported in study V130_03. Notably, the proportion of subjects who reported solicited local and systemic AEs was the same or lower in V130_12 compared with the previous trial. Geographic differences between the sites where the two studies were conducted (Europe and Asia in the case of V130_12 versus US for study 130_03) might be a possible explanation for this difference. Overall, no safety concerns or risks were observed from the QIVc studies and ongoing post marketing surveillance.
QIVc m2.5 addendum 2	QIVc study V130_10	In Study V130_10, subjects received QIVc or a US-licensed QIV, Afluria Quadrivalent, and overall rates of any solicited AEs were similar between the 2 vaccine groups. Solicited local AEs were reported after any vaccination by 41.9% of subjects in the QIVc group and 44.6% of subjects in the US-licensed QIV group; solicited systemic AEs were reported by 43.5% and 45.7% of subjects, respectively. For QIVc and US-licensed QIV, the most commonly reported local solicited AEs were tenderness and erythema; the most commonly reported

Source	Studies Summarized	Key Safety Outcomes
		systemic solicited AEs were irritability and sleepiness (27% and 26%, respectively). Fever (≥38.0°C) was reported by approximately 7% of subjects and the rates were similar between the QIVc and US-licensed QIV groups; fever (≥40.0°C) was rare (<1%). The rates of all-causality unsolicited AEs reported during the treatment period in Study V130_10 were similar between the QIVc (26%) and US-licensed QIV (26%) groups and most were mild or moderate in severity. The rates of unsolicited AEs related to the study vaccine were low in both vaccine The safety profile of QIVc in children 6 months through 47 months of age is generally consistent with that observed in previous pediatric studies with QIVc.
QIVc m2.5 addendum 3	V130_11OB	Study V130_11OB evaluated data from 665 prospectively enrolled evaluable women who had received QIVc during any trimester of pregnancy as part of routine care. The study found that >99% (95% CI: 98.0%-99.7%) of pregnancies resulted in live birth Prevalence rates for the infant outcomes reported from the study were low birth weight (5.8%), preterm birth (9.2%) and major congenital malformations (1.9%). The background rates reported in the general US population were 8.3%, 10.2% and 2.8%, respectively. Furthermore, no patterns in type of malformation were identified among the MCM reports and none of the MCMs were assessed as possibly related to timing of exposure to QIVc, supporting that there is no evidence of a teratogenic effect. The Study V130_11OB findings are consistent with analyses of data from pregnant women exposed to influenza vaccine reported in the VAMPSS (Vaccines and Medications in Pregnancy Surveillance System), VAERS (Vaccine Adverse Event Reporting System) and VSD (Vaccine Safety Database) which have found no evidence of meaningful increase in spontaneous abortion, preterm delivery, low birth weight or major congenital malformations (Chambers et al. 2016; Louik et al. 2016; Moro et al. 2017; Zerbo et al. 2017; Donahue et al. 2019).

The clinical development program to support registration of QIVc in individuals 9 years of age and above built on that of the TIVc development, which had demonstrated the safety, immunogenicity and efficacy of TIVc compared to licensed egg-based comparator.

Safety data from 2 clinical studies comparing QIVc with TIVc were 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 are provided unpooled.

In addition, safety data from 12 clinical studies performed with TIVc were 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.

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

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

Integrated safety is only reported from studies with unique exposures and therefore does not include extension studies.

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, including 1161 in the 4 to < 9 years age group and 1171 in the 9 to <18 years age group in study V130_03. 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 did not reach the numbers recommended in the "Guideline for the evaluation of new vaccines" (EMEA/CHMP/VWP/164653/2005). However, in the course of an earlier scientific advice (EMEA/CHMP/27711/2014) CHMP acknowledged that the higher HA antigen content of QIVc (60µg) compared to TIVc (45 µg) due to the addition of a fourth strain was unlikely to have an impact in the safety profile and agreed that it would be possible to extrapolate the adult safety database of the licensed TIVc. Consequently, a database of around 1300 adult subjects would be acceptable if no safety signals arise unique to QIVc. Moreover, later in the 2017 Scientific advice (EMA/CHMP/SAWP/99805/2017) it was stated that the total safety database was 2473 subjects (adults and paediatric population) and the CHMP response did not make any objection to this figure.

Therefore, the QIVc database of 1324 subjects ≥ 18 years of age and 1159 subjects 4 to <18 years was 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

Solicited 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.

Adult population-Subjects ≥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 ≥ 38.0oC) 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 few severe solicited AEs in any 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 profile 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. The applicant acknowledged these data but they were not considered a matter of concern regarding safety of QIVc since the reactions were generally mild to moderate in severity.

Paediatric population- Subjects 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 °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°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). The percentages of AEs judged by the investigator as possibly/probably related to the study vaccine were also higher in the entire paediatric group and more pronounced in the 4 to < 9 years of age subjects.

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 events, deaths, and 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 130_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 this 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.

Safety in special populations

Regarding 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 study. A question was raised regarding data on pregnant women and these data were provided and did not raise any safety concern.

Paediatric subjects 4 to <18 years of age with an increased risk of influenza associated complications were not analysed in the QIVc V130_03 study either.

Selected unsolicited AES indicating allergic reactions were analysed for the pooled adult and paediatric safety populations from TIVc studies. No information regarding allergic, hypersensitivity or immunological reactions in the QIVc studies was provided. These data were provided during the procedure and show no significant differences between QIVc and TIV1c/TIV2c treatment groups. No AEs related to the study vaccine led to discontinuation in QIVc adults' study. Nevertheless, 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).

Pregnancies and Safety during pregnancy

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, initially, not available. During the procedure the data have been provided and do not raise any safety concern.

As a post marketing commitment to FDA, Seqirus has initiated a prospective observational safety study to evaluate pre-specified outcomes among women immunized as part of routine care with TIVc or QIVc during pregnancy.

Safety related to drug-drug interactions and other interactions

The study V130_01 was not intended to measure drug interactions. However, in one study (V58P4E2) with TIVc, the data of seroconversion, seroprotection and GMTs showed no statistically significant differences in subjects who received TIVc alone or TIVc with pneumococcal vaccine. Concomitant use of the pneumococcal vaccine did not reduce the immune response of the TIVc vaccine.

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).

To support the extension of indication of Flucelvax Tetra, the description of the safety of Flucelvax tetra compared to a non-influenza comparator (Menveo) in children of 2 to <18 years of age was analysed in the clinical study V130_12.

Patient exposure

The *safety dataset for children* comprises data derived from 4514 subjects 2 to <18 years of age enrolled in V130_12 study. From these, 2258 subjects received QIVc. Approximately half of them (57.07%) were children between 2 to <9 years of age.

In the group of subjects 2 to <9 years of age, 32.8% of them had previously received one dose of influenza vaccine followed by one dose of the study vaccine. The rest of them, 763 subjects, had not been previously vaccinated against influenza vaccine and received two doses of the study vaccine separated by approximately 28 days.

All of the subjects 9 to <18 years of age (100%) were categorized as previously vaccinated against influenza and received 1 dose of the study vaccine or the comparator.

There was no notable difference in the distribution of demographic and baseline characteristics (age, sex, ethnic origin or country of enrolment) between the 2 vaccine groups.

Adverse events

Solicited Adverse Events

Solicited local and systemic AEs in subjects 2 to <18 years of age were recorded at 30 minutes following vaccination and from 6 hours through Day 7 after vaccination the use of analgesics/antipyretic for prophylaxis or treatment of fever (define as body temperature ≥38ºC, preferably measured orally) was evaluated.

The rates of solicited AEs reported within 30 minutes after any vaccination were low in subjects 2 to <18 years of age, being reported as slightly higher in the QIVc group (9.5%) compared to the comparator group (7.3%).

The percentage of subjects with any solicited AE reported from Day 1 through Day 7 after vaccination was 51.4% in the QIVc and 48.6% in the comparator group. The rates of local and systemic solicited AEs were similar in each vaccine group.

Table 53 Number (5) of subjects 2 to <18 years of age with at least one solicited adverse event 30 minutes postvaccination and/or day 1 (6 hours) through 7 days after any vaccination-solicited safety set

Solicited Adverse Event	QIVc N=2255 n (%)	Comparator N=2254 n (%)
30 Minutes After Any Vaccination		
Any	214 (9.5)	165 (7.3)
Local	202 (9.0)	157 (7.0)
Systemic	19 (0.8)	16 (0.7)
Others[a]	5 (0.2)	3 (0.1)
6 Hours on Day 1 Through 7 Days After Any Vaccination		
Any	1159 (51.4)	1096 (48.6)
Local	829 (36.8)	757 (33.6)
Systemic	707 (31.4)	688 (30.5)
Others[a]	195 (8.6)	164 (7.3)

Solicited Local Adverse Events

The percentage of subjects with any solicited local AE reported from Day 1 (6 hours) through Day 7 after vaccination was 36.9% in the QIVc group and 33.6% in the comparator group (Table 53). No notable differences in the rate of solicited local AEs were observed between the QIVc and the comparator, except for a slightly higher rate of pain observed in the QIVc (23.8% in QIV group *vs* 19.0% in comparator group), but a slightly lower rate of induration and erythema observed in the QIVc group vs the comparator. The most commonly reported solicited local AEs were tenderness, pain and erythema; the majority were mild to moderate in severity (the proportion of subjects with severe local AEs in OIVc groups was ≤1%). See Table 54.

Table 54 Number (%) of Subjects 2 to < 18 Years of Age with Solicited Local Adverse Events from 6 Hours Through 7 Days After Any Vaccination – Solicited Safety Set

Solicited Local Adverse Event	QIVc N=2255 n (%)	Comparator N=2254 n (%)
Induration (mm)	N=2246	N=2239
Any	286 (12.7)	294 (13.1)
Severe[a]	3 (0.1)	7 (0.3)
Erythema (mm)	N=2246	N=2242
Any	433 (19.3)	476 (21.2)
Severe[a]	4 (0.2)	17 (0.8)
Ecchymosis (mm)	N=2244	N=2240
Any	169 (7.5)	142 (6.3)
Severe[a]	0 (<0.1)	1 (<0.1)
Pain[b]	N=1658	N=1679
Any	395 (23.8)	319 (19.0)
Severe	12 (0.7)	20 (1.2)
Tenderness[b]	N=578	N=562

Solicited Local Adverse Event	QIVc N=2255 n (%)	Comparator N=2254 n (%)
Any	166 (28.7)	143 (25.4)
Severe	6 (1.0)	8 (1.4)

Source: Section 5.3.5.1, CSR V130_12 Table 12-4.

Abbreviations: QIVc = cell derived quadrivalent subunit influenza virus vaccine.

[a] For induration, ecchymosis, and erythema, >50 mm is severe for subjects 2 to <6 years of age, and >100 mm is severe for subjects ≥6 years of age.

[b] Tenderness was collected on the subject diary card for subjects 2 to <6 years of age, whereas pain was collected on the subject diary card for subjects ≥6 years of age.

Note 1: The non-influenza comparator is meningococcal (Serogroup ACWY) conjugate vaccine. Previously vaccinated subjects under 9 years of age received 1 vaccination (QIVc or Men ACWY) on Day 1. For subjects under 9 years of age who had not been previously vaccinated, 2 vaccinations were administered; the comparator vaccine group received Men ACWY on Day 1 followed by a saline placebo vaccine on Day 29, whereas the QIVc group received 2 QIVc vaccinations on Days 1 and 29.

Note 2: Solicited adverse events displayed include those reported from 6 hours postvaccination through 7 days after vaccination.

Solicited Systemic Adverse Events

The percentage of subjects 2 to <18 years of age with any solicited systemic AE reported from Day 1 (6 hours) through Day 7 after vaccination was 31.4% in the QIVc group and 30.5% in the comparator group (Table 53). No notable differences in the rate of solicited systemic AEs were observed between the QIVc and the comparator. The most commonly reported solicited systemic AEs were headache, feeling fatigue or tiredness; the majority were mild to moderate in severity (the proportion of subjects with severe systemic AEs in QIVc groups was ≤1%).

The proportion of subjects reporting solicited systemic AEs after any vaccination was lower in the previously vaccinated subjects, compared to the group that had received two doses of QIVc. Additionally, in this group, the solicited systemic AEs were reported as slightly lower after the second dose than after the first dose of QIVc.

Table 55 Number (%) of Subjects 2 to < 18 Years of Age with Solicited Systemic Adverse Events from 6 Hours Through 7 Days After Any Vaccination – Solicited Safety Set

Solicited Systemic Adverse Event	QIVc N=2255 n (%)	Comparator N=2254 n (%)
Loss of appetite[a]	N=1674	N=1685
Any	154 (9.2)	129 (7.7)
Severe	8 (0.5)	9 (0.5)
Nausea (feeling the need to vomit)[a]	N=1668	N=1684
Any	95 (5.7)	93 (5.5)
Severe	2 (0.1)	11 (0.7)
Muscle aches all over the body[a]	N=1668	N=1683
Any	84 (5.0)	84 (5.0)
Severe	7 (0.4)	8 (0.5)
Aching in several joints[a]	N=1669	N=1682
Any	108 (6.5)	129 (7.7)
Severe	6 (0.4)	8 (0.5)
Headache[a]	N=1668	N=1685
Any	278 (16.7)	261 (15.5)
Severe	17 (1.0)	10 (0.6)
Feeling fatigue or tiredness[a]	N=1669	N=1684

Solicited Systemic Adverse Event	QIVc N=2255 n (%)	Comparator N=2254 n (%)
Any	265 (15.9)	274 (16.3)
Severe	17 (1.0)	17 (1.0)
Shivering/chills[b]	N=2249	N=2248
Any	145 (6.5)	128 (5.7)
Severe	11 (0.5)	7 (0.3)
Loose stools or diarrhea	N=2249	N=2250
Any	156 (6.9)	168 (7.5)
Severe	10 (0.4)	10 (0.4)
Vomiting or throwing up	N=2250	N=2248
Any	89 (4.0)	80 (3.6)
Severe	10 (0.4)	11 (0.5)
Change in eating habits[c]	N=578	N=564
Any	57 (9.9)	57 (10.1)
Severe	6 (1.0)	4 (0.7)
Sleepiness[c]	N=578	N=564
Any	86 (14.9)	99 (17.6)
Severe	5 (0.9)	10 (1.8)
Irritability[c]	N=578	N=564
Any	80 (13.8)	61 (10.8)
Severe	1 (0.2)	3 (0.5)
Fever	N=2247	N=2242
Any (>=38.0°C)	118 (5.3)	102 (4.5)
>=40.0°C	7 (0.3)	5 (0.2)

Source: Section 5.3.5.1, CSR V130_12 Table 12-10.

Fever (≥38ºC) was reported by 5.3% and 4.5% in QIVc and comparator group, respectively. The proportion of subjects using analgesics/antipyretics after any vaccination for prevention or treatment of pain/fever was similar for the QIVc (6.0% and 6.2%, respectively) and for the comparator groups (5.0% and 4.8% respectively).

Unsolicited Adverse Events

Unsolicited Adverse Events were reported spontaneously through Day 22 or 50 depending on whether they received 1 or 2 vaccinations.

The rates of unsolicited AEs in subjects 2 to <18 years of age during the treatment period was similar in the QIVc group and in the comparator group. Only 4.3% and 3.9 % were considered to be at least possibly related to the study vaccine and comparator vaccine by the investigator. See Table 56.

Table 56 Overall Summary of Reportable Treatment-Emergent Unsolicited Adverse Events in Subjects 2 to < 18 Years of Age - As Treated - Overall Safety Set

	QIVc N=2258 n (%)	Comparator N=2255 n (%)
Any AE (Day 1 - Day 22/50[a])	633 (28.0)	630 (27.9)
Any AE by severity		
Mild	550 (24.4)	555 (24.6)
Moderate	109 (4.8)	101 (4.5)
Severe	11 (0.5)	11 (0.5)
Related AE	97 (4.3)	89 (3.9)
SAE	25 (1.1)	30 (1.3)
Related SAE	0	0
AE leading to study withdrawal	0	0
Medically-attended AE[b]	614 (27.2)	679 (30.1)
NOCD	9 (0.4)	11 (0.5)
Death	0	1 (<0.1)

Source: Section 5.3.5.1, CSR V130_12 Table 12-3

The number (%) of subjects 2 to < 18 years of age who reported unsolicited AEs that were considered to be at least possibly related to the study vaccination, observed in >1% in QIVc group, were Influenza like illness (1.1%). Other unsolicited AEs considered as related to the study vaccine were reported as less than 0.7% (Upper respiratory tract infection, rhinitis, rhinorrhoea, cough and nasopharyngitis).

Serious adverse event/deaths/other significant events

SAEs, deaths and other significant events (new onset of chronic disease, events leading to withdrawal and medically-attended AEs within 30 days after the onset) were collected for up 6 months after the last vaccination.

SAEs

In total, 25 (1.1%) subjects in the QIVc group and 30 (1.3%) subjects in the comparator group reported SAEs after any vaccination with onset from Day 1 through end of study. No SAEs were assessed as related to vaccination.

Deaths

One death occurred in a subject who had received the comparator vaccine.

Other significant events

No AEs leading to withdrawal from the study were reported.

The proportion of subjects who reported medically attended unsolicited AEs and reported AE leading to NOCD was similar for both vaccine groups. None of the AEs leading to new onset of chronic disease was considered to be related to the study vaccine.

2.5.8.1. Safety in special populations

Intrinsic factors

By Age

In the analysis by age subgroups, solicited AEs data were analysed stratified in subjects 2 to < 6, 6 to < 9, and 9 to < 18 years of age. Unsolicited AEs were analysed by age groups of 2 to < 9 and 9 to < 18 years of age.

Solicited AEs:

In the analysis by age subgroups, the proportion of subjects with any solicited local AEs within 30 minutes after any vaccination was low for the QIVc (04%-1.4%) and the comparator group (0.7% - 1.4%) in all age subgroups. The most commonly reported local solicited AEs after 7 day following any vaccination for both vaccine groups were tenderness (in the 2 to <6 years aged group), pain (in the 6 to <9 years aged group and in 9 to <18 years aged group) and erythema in all age groups. Additionally, the older children (9 to <18 years of age) reported overall a slightly lower percentage of solicited AEs compared to the younger children (including pain).

In both vaccine groups, the proportion of subjects (in 2 to <6, and in 6 to <9 years of age group) who had not been previously vaccinated with influenza vaccine reported lower solicited local AEs after the second vaccination than after the first vaccination with QIVc.

Regarding the solicited systemic AEs, the proportion of subjects with any solicited systemic AEs within 30 minutes after any vaccination was low. No notable differences for the QIVc and the comparator group were observed in all age subgroups. The most commonly reported systemic solicited AEs 7 days after any vaccination were sleepiness and irritability in the 2 to <6 age group; in the other age groups the most commonly reported systemic solicited AEs were headache and feeling fatigue or tiredness. In all age group, the incidence of these solicited AEs was <1% in the QIVc and the comparator group.

Additionally, the older children (9 to <18 age group) reported slightly lower rates of fever (≥38ºC) compared to the younger children (2.8%, 6.4% and 8.8% in 9 to <18, 6 to <9 and 2 to <6 age group, respectively).

Unsolicited AEs:

The proportion of subjects with any unsolicited AEs and any possibly related unsolicited AEs was lower in older subjects (18.1% and 2.6%) compared to the younger subjects (37.7% and 5.9%) in the QIVc group.

By gender

No notable differences in frequency of subjects 2 to <18 years of age reporting any local or systemic solicited AEs and unsolicited AEs were found between genders.

By racial/ethnic origin

The proportion of subjects 2 to <18 years of age reporting any solicited local and systemic AEs was higher in White subjects than in Asian subjects in both vaccine groups. The proportion of subjects with unsolicited AEs was similar in Asian and White subjects. The numbers of subjects from other racial origin were too small to make a meaningful comparison

Extrinsic Factor

By vaccination status

In subgroup 2 to 6 years of age and 6 to 9 years of age the vaccine scheme was defined for influenza vaccination status. The previously vaccinated subjects received 1 dose and the non-previously vaccinated received 2 doses of QIVc.

All of the subject 9 to <18 years of age (100%) were categorized as previously vaccinated against influenza and received 1 dose of the study vaccine or the comparator. With respect to solicited local and systemic AEs, the proportion of subjects with solicited AEs after any vaccination was lower in the "previously vaccinated" group than in the "not previously vaccinated" group. In both vaccine groups, the proportion of "not previously vaccinated" with any solicited AEs was lower after the second vaccination than after the first vaccination.

Regarding the Unsolicited AEs, a lower proportion of subjects reporting unsolicited AEs was found in the "previously vaccinated" subjects than in the "not previously vaccinated" group.

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

Co-administration of vaccines was not investigated in the study.

2.5.8.2. Post marketing experience

TIVc was first granted marketing approval in the EU via the centralized procedure on 01 Jun 2007, for use in adults 18 years of age and older. The US FDA granted marketing approval for use in persons 18 years of age and older on 20 November 2012. In the US, marketing approval for use in persons 4 to less than 18 years of age was also granted on 23 May 2016. The most recent Periodic Safety Update Report (PSUR) authored for TIVc, prior to discontinuation of the product, was PSUR 18 dated 26 April 2017, covering the period from 16 March 2016 to 15 March 2017. At the Data Lock Point (DLP) of PSUR 18 TIVc was registered in 33 countries worldwide. As summarized in PSUR 18, based on the postmarketing data presented in the report and the cumulative experience through to the data lock point, no new safety signals were identified and the benefit risk profile remained unchanged and favourable.

QIVc was first approved in the US for prevention of influenza in adults and children 4 years of age and older on 23 May 2016. On 12 Dec 2018, QIVc was approved in the EU for use in adults and children from nine years of age and on 22 October 2020 QIVc was approved in the EU for use in adults and children from 2 years of age.

Adverse events are monitored per QIVc routine pharmacovigilance activities. As summarized in the most recent QIVc PSUR (PSUR 6, covering the period 16 March 2023 to 15 March 2024), postmarketing experience with QIVc has not identified any safety concerns.

Whilst TIVc was licensed in the EU for use in adults 18 years of age and older, QIVc was licensed for use in adults and children from 2 years of age in the EU, and in adults and children 6 months of age and older in the US and several other countries. No new safety concerns for QIVc have been identified through safety monitoring in clinical trials and in the postmarket setting for children 6 months to 4 years of age.

The marketing experience for both TIVc and QIVc to date was consistent with the favourable safety and tolerability profile demonstrated in the clinical development program for TIVc and QIVc.

2.5.9. Discussion on clinical safety

The safety assessment of Flucelvax (TIVc) is mainly based in the data generated during development of the QIVc vaccine.

The initial Marketing authorisation for QIVc was based on three scientific advices presented to CHMP, and was based on the previous TIVc development, which demonstrated safety, immunogenicity and efficacy when compared to licensed egg-based comparator (TIVe).

Safety data from 2 clinical studies comparing QIVc with TIVc were included. Both studies (Study V130_01, Study V130_03) were phase 3 trials conducted in the US; one of them in adults 18 years of age and above (including elderly adults); and the second, 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.

Additionally, safety data from 12 clinical studies performed with TIVc were 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 was similar to the egg-based comparator trivalent influenza vaccines.

The total size of QIVc safety database did not reach the numbers recommended in the "Guideline for the evaluation of new vaccines" (EMEA/CHMP/VWP/164653/2005). However, in the course of an earlier scientific advice (EMEA/CHMP/27711/2014) CHMP agreed that it would be possible to extrapolate the adult safety database of the licensed TIVc. Consequently, a database of around 1300 adult subjects would be acceptable if no safety signals arose unique to QIVc. Moreover, later in the 2017 Scientific advice (EMA/CHMP/SAWP/99805/2017) it was stated that the total safety database was 2473 subjects (adults and paediatric population).

Therefore, the QIVc database of 1324 subjects ≥ 18 years of age and 1159 subjects 4 to <18 years was supported by the safety data set from TIVc studies.

In the study V130_01 a total of 2680 adults 18 years of age and above were enrolled, 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.

In study V130_03 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. 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 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 single geographical location, USA. Similar numbers of subjects were included in the different groups.

Solicited Adverse events

In adults ≥18 years of age, similar rates of solicited events were observed between QIVc and TIVc, and the majority of solicited reactions were mild to moderate in severity. There were few severe solicited AEs in any group, all of them were reported to be below 1% in the QIVc group.

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 ≥ 38.0oC) were low and similar across vaccine groups (0.5%, 0.7%, and 0.5%).

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%) reactions in adults in the QIVc group were injection-site pain (45.4%), followed by headache (18.7%), fatigue (17.8%), myalgia (15.4%), injection-site erythema (13.4%), and induration (11.6%).

The most common reactions in the elderly were injection-site pain (21.6%) and injection-site erythema (11.9%); headache, fatigue, myalgia 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 was similar to what had been observed with TIVc and TIVe comparator vaccines.

It is important to mention that 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). The applicant acknowledged these data but they were not considered a matter of concern regarding the safety of QIVC, since the reactions were generally mild to moderate in severity.

In the paediatric population, similar percentages of subjects 4 to < 18 years of age reported any solicited local AE and most of them were mild to moderate in severity, and had their onset from 6 hours to 2 days after the vaccination. 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 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.

In general, severe local solicited AEs in QIVc group were infrequent and reported in similar percentages to TIVc vaccines. In subjects 4 to < 9 years of age who received QIVc vaccine, severe injection site pain was reported by 1%, severe injection site tenderness was reported by 2%, severe erythema and induration were reported by ≤ 1%. In subjects to 9 < 18 years of age who received QIVc vaccine there were no severe solicited local AEs experienced by > 1%.

The percentages of subjects who reported individual solicited systemic AEs were mostly similar across the QIVc, TIV1c, and TIV2c vaccine groups except 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 QIVc vaccine group was irritability (2%). Fever (≥ 38.0ºC) 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°C in the QIVc group.

Unsolicited Adverse events

The percentage of unsolicited AEs reported in the adult population in the treatment period (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). 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). The percentages of AEs judged by the investigator as possibly/probably related to the study vaccine were also higher in the entire paediatric group and more pronounced in the 4 to < 9 years of age subjects.

According to the applicant, this may be partly due by a longer observation period in subjects not previously vaccinated against influenza, however the higher percentage of unsolicited AEs was also observed in the 9 to > 18 years of age subgroup that only received one vaccination.

Selected unsolicited AEs indicating allergic reactions were analysed for the pooled adult and paediatric safety populations from TIVc studies. No information regarding allergic, hypersensitivity or immunological reactions in the QIVc studies was provided. During the procedure, the applicant provided the results, and they showed no significant differences between QIVc and TIV1c/TIV2c treatment groups.

Serious adverse events and deaths

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.

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 this 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).

Safety in special populations

Safety in special populations (immunocompromised individuals, pregnant, breast-feeding women or paediatric subjects with an increased risk of influenza associated complications) were not analysed. All of these were considered as an exclusion criteria in the QIVc study and this should be included as missing information. However, 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 not available. Data were provided during the procedure and did not raise any safety concern.

As a post marketing commitment to FDA, Seqirus has carried out a prospective observational safety study to evaluate pre-specified outcomes among women immunized as part of routine care with TIVc or QIVc during pregnancy.

The study V130_01 was not intended to measure drug interactions. However, in one study (V58P4E2) with TIVc, the data of seroconversion, seroprotection and GMTs showed no statistical significant differences in subjects who received TIVc alone or TIVc with pneumococcal vaccine. Concomitant use of the pneumococcal vaccine did not reduce the immune response of the TIVc vaccine.

In summary, 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. There were more individual unsolicited AEs experienced by > 1% of in subjects 4 to < 18 years of age (and more pronounced in the 4 to < 9 years of age subjects) across all 3 vaccine groups when comparing with the adult population QIVc studies. No SAEs, NOCD and deaths in paediatric and adult populations were judged by the investigator as possibly/ probably related to the study vaccines. Safety in special populations and drug interactions have not been analysed in QIVc studies.

To support the extension of indication for the QIVc vaccine , the MAH provided the data of study V130_12. The description of the safety of QIVc was compared to a non-influenza comparator (Menveo) in children of 2 to <18 years of age.

The safety database in V130_12 was of 4514 subjects 2 to <18 years of age. From these, 2258 subjects received QIVc. Approximately half of them (57.07%) were children between 2 to <9 years of age. In 2 to >9 years of age, 67.2% (763 subjects) had not been previously vaccinated against any influenza vaccine and received two doses of the study vaccine separated by approximately 28 days. The rest of children 2 to >9 and all 9 to >18 years of age received one dose of the study vaccine.

The rates of reported solicited local and systemic AEs during the treatment period (recorded at 30 minutes following vaccination and from 6 hours through Day 7 after vaccination) were comparable between the 2 vaccine groups in subjects 2 to <18 years of age.

The rates of solicited AEs reported within 30 minutes after any vaccination were reported as low but slightly higher in the QIVc group (9.5%) compared to the comparator group (7.3%). The percentage of subjects with any solicited AE reported from Day 1 through Day 7 after vaccination was 51.4% in the QIVc and 48.6% in the comparator group. Regarding the solicited local AEs, similar rates were observed in each vaccine group (36.9% in the QIVc group and 33.6% in the comparator group), as no notable differences were observed between the QIVc and the comparator. Nevertheless, a slightly higher rate of pain, but a slightly lower rate of induration and erythema was reported in the QIVc group vs the comparator. The most commonly reported solicited local AEs were erythema, pain and tenderness; the majority were mild to moderate in severity.

Regarding the solicited systemic AEs, similar rates were reported in each vaccine group (31.4% in the QIVc group and 30.5% in the comparator group) as no notable differences were observed between the QIVc and the comparator. Nevertheless, a slightly higher rate of headache, but a slightly lower rate of feeling fatigue or tiredness was reported in the QIVc vs the comparator group. The most commonly reported solicited systemic AEs were headache, feeling fatigue or tiredness and the majority were mild to moderate in severity. Fever (≥38ºC) was reported by 5.3% and 4.5% in QIVc and comparator group, respectively.

The rates of unsolicited AEs, were comparable between the 2 vaccine groups in the subjects of 2 to <18 years of age. Only 4.3% and 3.9 % were considered to be at least possibly related to the study vaccine and to the comparator vaccine by the investigator.

In the subgroup analysis by age, the proportion of subjects with any solicited local and systemic AEs within the 30 minutes after any vaccination were low and comparable in both vaccine groups in all age subgroups. Additionally, the older children (9 to <18 years of age) reported overall slightly lower percentage of solicited local and systemic AEs within the 30 minutes after vaccination compared to the younger children.

As requested during the procedure, the solicited AEs (local and systemic) rates from 6 hours through Day 7 after any vaccination, stratified by the different age subgroups (2 to <6, 6 to <9 and 9 to <18), to establish comparisons in terms of reactogenicity between the study vaccine and the comparator in the different age groups were provided. Overall, no notable differences in the rate of solicited local and systemic AEs were observed between the QIVc and the comparator in any age subgroup. Only, a slightly higher rate of tenderness in the QIVc in 2 to <6 yoa subjects and a slightly higher rate of pain, chills, headache and body temperature ≥38.0ºC in the QIVc group in 6 to <9 yoa group was reported. The majority of the reported solicited local and systemic AEs in any age group were mild to moderate in severity. The table from SmPC reporting the data from both studies V130_12 and V130_03 was updated by the MAH. Additionally, the older children (9 to <18 years of age) reported overall a slightly lower percentage of solicited AEs compared to the younger children. Thus, the issue raised is considered as solved

Comparing the rates reported by any solicited AEs in the new V130_12 study in subjects 2 to < 18 years of age to the study V130_03 performed in 4 to <18 years of age group, the data observed in the QIVc group were lower in the new study (51.4% and 72% respectively). This difference was mainly observed in the solicited local AEs, whereas the rates were much lower in the new V130_12 than in the reported before (36.9% and 66% in V130_12 and V130_03 respectively). No notable difference in the rates regarding solicited systemic AEs was found between these studies (31.4% and 38% in V130_ 12 and V130_03 respectively).

Since a large difference was observed between the two studies provided to support the indication of QIVc in children, mainly due to the different rates reported for the local solicited AEs, a clarification was requested to the MAH during the procedure. The applicant explained that the differences in the rates observed were associated to ethnicity. This effect was observed in both QIVc and comparator

groups in the study V130_12. The justification provided by the applicant was found acceptable and the issue was considered as solved. The proportion of subjects with any unsolicited AEs and any possibly related unsolicited AEs was lower in the older subjects (18.1% and 2.6%) compared to the younger subjects (37.7% and 5.9%) in the QIVc group. By gender, no notable differences in the frequency of solicited or unsolicited AEs were observed. By racial/ethnic origin, only a comparison between Asian and white population was made, as the numbers of subjects from other racial origin were too small to make a meaningful comparison. The proportion of subjects 2 to <18 years with any solicited local and systemic AEs were higher in White subjects than in Asian subjects in both vaccine groups. The proportion of subjects with unsolicited AEs was similar in Asian and White subjects.

When considering the vaccination status, the proportion of subjects with any solicited and unsolicited AEs after any vaccination was lower in the "previously vaccinated" group than in the "not previously vaccinated" group, in both subgroups 2 to 6 years of age and 6 to 9 years of age. The proportion of subjects with any solicited AEs was lower after the second vaccination in the "not previously vaccinated" group than after the first vaccination in both vaccine groups.

No SAEs (1.1% and 1.3% in QIVc and comparator group, respectively) and deaths (one in comparator group) reported were assessed as related to the vaccination with the study vaccine. No AEs leading to withdrawal from the study were reported after the vaccination with QIVc.

Discussion of supportive QIVc study (V130_11OB)

Regarding supportive studies, the data and results from the observational study Study V130_11OB was considered for the analysis of the risk during pregnancy. This prospective pregnancy registry V130_11OB "Use in pregnant and breastfeeding women" was required by the FDA and included pregnant women within the US who were immunized as part of routine care with the TIVc or QIVc vaccine at any time during pregnancy.

Main objectives were to evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunised as part of routine care with the seasonal TIVc or QIVc vaccine during pregnancy

Of the evaluable 665 exposed pregnancies, 659 resulted in live births, with 667 infants born. There were no stillbirths. Of the prospectively enrolled women, 196 (28.3%) were exposed during their first trimester of pregnancy, 286 (41.3%) during the second trimester and 211 (30,4%) during the third trimester. Of the 665 women in the PAP, 211 (31.7%) were enrolled in the study prior to 20 weeks gestation. Prevalence rates for the infant outcomes of low birth weight (5.8%), preterm birth (9.2%) and major congenital malformations (1.9%), were below the rates reported in the general US population of 8.3%, 10.2% and 2.8%, respectively (Correa et al 2007; Martin et al. 2019; Martin et al. 2020). There was no pattern regarding the MCMs.

Based on pregnancy outcomes and predefined infant safety outcomes, there was no evidence of adverse fetal, newborn or pregnancy outcomes attributable to the vaccine during any stage of pregnancy. Moreover, study findings are consistent with analyses of data from pregnant women exposed to influenza vaccine reported in the VAMPSS (Vaccines and Medications in Pregnancy Surveillance System), VAERS (Vaccine Adverse Event Reporting System) and VSD (Vaccine Safety Database) which have found no evidence of meaningful increase in spontaneous abortion, preterm delivery, low birth weight or major congenital malformations. The findings were also consistent with the relevant clinical experience with seasonal influenza vaccines similar to the drug product during pregnancy.

In summary, the safety assessment of TIVc (Flucelvax) is based on the data generated during the development of QIVc (Flucelvax tetra). Data for QIVc are relevant to TIVc because both vaccines are manufactured using the same process and have overlapping compositions. The warnings, recommendations and contraindications that currently apply to QIVc do also apply to TIVc.

After the review of the data submitted, specifically the studies V130_01 and V130_03, the TIVc safety profile is in general comparable to QIVc. No new safety signal was seen in the submitted clinical database. The safety profile of TIVc is considered as adequate.

Moreover, QIVc was well tolerated, showing a good safety profile in subjects 2 to <9 years of age (data from V130_12) with, in general, a comparable safety profile to a non-influenza comparator vaccine. Therefore, considering that QIVc and TIVc were comparable in terms of safety profile and with a similar pattern in subjects aged ≥9 years, it is expected that TIVc will be well tolerated in subjects aged 2 to <9 years.

Additionally, the safety data available from 12 clinical studies performed with TIVc, show results similar to TIVe, and support the safety profile of this TIVc vaccine

The post marketing experience of TIVc, prior to discontinuation of the product, indicated that no new safety signals were identified. In the same line, the post-marketing experience with QIVc (since its first approval) has not identified any safety concerns.

2.5.10. Conclusions on the clinical safety

The CHMP concludes that the clinical safety data supports the indication of prophylaxis of influenza in adults and children from 2 years of age.

2.6. Risk Management Plan

2.6.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety in immunocompromised patients Safety in subjects with underlying diseases

2.6.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Additional pharmacovigilance activities recommended under EMA guidelines				
A non-interventional study of vaccine effectiveness; TIVc/QIVc versus no vaccination (DRIVE subanalysis)	To perform an analysis of influenza vaccine effectiveness of TIVc/QIVc vaccination versus no vaccination in persons of an age aligned with the applicable age indication	None	Conducted annually during the influenza season	First annual availability of results planned before Q4 2020 and annually thereafter

2.6.3. Risk minimisation measures

Safety concern	Routine risk minimisation activities
Important identified risks: None	
Important potential risks: None	
Missing Information:	
Safety in immunocompromised patients	Routine risk communication: Summary of Product Characteristics (SmPC) Section 4.4 Package Leaflet (PL) Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None
Safety in subjects with underlying diseases	Routine risk communication: SmPC Section 4.4 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 3.2 is acceptable.

In addition, the following minor revisions are recommended to be taken into account with the next RMP update:

- The MAH is requested to remove the missing information Safety in immunocompromised patients and Safety in subjects with underlying disease from the Summary of safety concerns.
- Considering that DRIVE is not addressing a safety concern in the RMP and relates to effectiveness, the project should be removed as an additional pharmacovigilance activity in the RMP. However, the MAH is expected to provide regular updates and results on the project in PSURs.

2.7. Pharmacovigilance

2.7.1. 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.

2.7.2. Periodic Safety Update Reports submission requirements

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.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

CSL Seqirus completed a consultation with target patient groups (user testing) on the Flucelvax Tetra (QIVc) Package Leaflet (PL) and submitted the results (final report dated, 06 April 2018), as part of the initial EU marketing authorization application (MAA) that was approved on 12 Dec 2018 (with the age indication from 9 years and older). The results of the user consultation with target patient groups met the criteria for readability as described in the Guideline on the readability of the label and package leaflet of medicinal products for human use. Subsequently, a type II variation to extend the indication in the paediatric population to the current indication of 2 years of age and older was and approved on 22 October 2020. As part of the procedure, justification for not performing additional user testing was provided and found to be acceptable. As part of the current application for the Flucelvax Trivalent (TIV) formulation, CSL Seqirus proposes to maintain alignment of the Flucelvax TIV PL with the currently approved Flucelvax QIV PL with only minor changes being proposed to replace the QIV product name with the TIV product name. No changes to the indicated population, safety data or use of the vaccine

have been proposed. CSL Seqirus considers that the previously conducted user testing conducted for the QIV product is relevant to the TIV product and further, given no content changes have been proposed in the TIV PL, that conducting new consultation with target patient groups on the TIV PL is not required as part of the current application.

As part of the current application, Summary of Product Characteristics (SmPC) and Package Leaflet (PL) have been created starting from the existing QIVc SmPC and PL with only minor modifications in the PL.

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. Influenza type B viruses are classified into 2 distinct genetic lineages, Yamagata and Victoria; however, the B/Yamagata lineage has not been confirmed to be in circulation since March 2020.

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 4 influenza strains in their composition, 2 influenza A strains (largely A/H1N1 and A/H3N2), and 2 influenza B strains

(B/Yamagata and B/Victoria). However, the B/Yamagata lineage circulation has not been confirmed since March 2020. Therefore, the risk of infection with B/Yamagata is considered low and its inclusion in quadrivalent influenza vaccines is considered to be unnecessary. The World Health Organisation (WHO) made the recommendation to exclude B/Yamagata from quadrivalent influenza vaccine compositions as soon as possible.

Other 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 efficacy assessment of Flucelvax (TIVc) is mainly based in the data generated during development of the QIVc (Flucelvax tetra) during the MAA (EMEA/H/C/004814) and during the extension of indication variation (number procedure EMEA/H/C/004814/II/0013). This comprises five studies. These, together with the Optaflu (TIVc) efficacy study, are considered pivotal:

- Two phase III immunogenicity studies comparing QIVc and TIVc in adults (V130_01) and children 4 to 18 years of age (V130_03), assessed as part of the initial MAA of Flucelvax Tetra (QIVc), supporting the initial indication from 9 years of age.
- One phase III/IV efficacy and immunogenicity study in children 2 to 18 years of age (V130_12), assessed as a variation of Flucelvax Tetra (QIVc), supporting an extension of indication in children from 2 years of age.
- One phase III immunogenicity study in children 6 to 47 months of age (V130_10), assessed as a post-authorization measure to Flucelvax Tetra (QIVc).
- One phase III immunogenicity and efficacy study in adults (V58P13) assessed as a post-authorization measure for Optaflu (TIVc)

There are other studies carried out during the development of the previous TIVc, whose relevance is limited and are only considered supportive in the context of this MAA.

- One phase II/III immunogenicity study comparing TIVc to a TIV produced in embryonated eggs in children (V58P12).
- One phase I/II dose-finding study in children 6-48 months of age that did not result in any dose selection, study V58P16. This study is not considered relevant in terms of efficacy for the current application.
- 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 (V58P15, V58-31, V58P16).

3.2. Favourable effects

The submitted efficacy data from study V130_12 demonstrate that QIVc is efficacious in preventing influenza in children 2 to < 18 years and in children 3 to < 18 years of age. The observed VE in subjects 2 to < 18 years of age (primary endpoint) was 54.63%, and the lower bound of the 95% CI was greater than 20% (95% CI: 45.67; 62.12). The observed VE in subjects 3 to < 18 years of age (co-primary endpoint) was 54.03%, and the lower bound of the 95% CI was greater than 30%. All secondary endpoints were consistent with the primary study endpoint.

The submitted efficacy data from study V58P13 demonstrate that previous TIVc is efficacious in preventing influenza in adults. The observed VE for vaccine-matched strains was 83.8%, with the lower bound of the 95% CI being 61%. The observed VE for all confirmed influenza was 69.5%, with the lower bound of the 95% CI being 55%.

Efficacy has been therefore demonstrated in adults for the previous TIVc, and in children from 2 years of age in QIVc, the tetravalent vaccine manufactured like Flucelvax and that only differs in the presence of B/Yamagata HA.

Other studies like V130_01, V130_03, V130_10 and V58P12 consistently show that the vaccine, whether in trivalent or tetravalent form is immunogenic, eliciting HI antibodies.

The previously authorized TIVc was authorized through the centralized procedure in 2007 and was marketed until the switch to tetravalent vaccines, when Flucelvax Tetra (QIVc) was authorized in 2018. This results in more than 15 years of experience with these products.

The efficacy profile of previous TIVc and QIVc are applicable to Flucelvax because they are produced using the same cell culture manufacturing platform and they have the same formulation and dosage, except for the removal of B/Yamagata antigen after this strain is no longer circulating.

Therefore, it is concluded that clinical efficacy/immunogenicity data supports an indication in adults and children from 2 years of age.

3.3. Uncertainties and limitations about favourable effects

No new clinical studies have been performed to support the Marketing Authorisation for Flucelvax trivalent formulation (TIVc). The clinical efficacy of Flucelvax (TIVc) is based on the extrapolation of the documented efficacy of Flucelvax Tetra and the previously authorized TIVc vaccine (Optaflu). Nevertheless, it is considered that studies performed with Optaflu and Flucelvax tetra provide reliable information about the favourable effects of Flucelvax.

Virus neutralization data were generated only as an exploratory endpoint in the comparative immunogenicity study in children 6 to 47 months of age. However, the data has been used as an alternative to HI assay for assessing the primary endpoint for the A/H3N2 strain.

Concomitant administration with other vaccines in elderly has been evaluated with the previous TIVc vaccine; results for the co-administration with pneumococcal vaccine did not meet the non-inferiority criteria, presumably due to small sample size. Also, co-administration with other vaccines recommended in elderly (i.e. Covid-19, RSV, Herpes Zoster) has not been studied.

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 TIVc, show reduced efficacy (in terms of immunogenicity) in the elderly due to immune senescence.

3.4. Unfavourable effects

The safety assessment of Flucelvax (TIVc) was based on the data generated during the development of QIVc, during the iMAA and during the extension of indication.

According to the data submitted, the rates of solicited events (local and systemic) in both children (>4 years of age) and adults, were similar between TIVc and QIVc, and the majority of solicited reactions were mild to moderate in severity. Therefore, the overall safety profile of TIVc (used as comparator vaccine) was comparable to the cell-based tetravalent influenza vaccine.

The percentage of unsolicited AEs (related and non-related) reported was similar in the QIVc, TIV1c, and TIV2c groups for both adult and paediatric population, with higher frequencies in younger than in older subjects. Results in adults are comparable to results reported in the pooled exposed safety population with TIVc.

The reporting data of solicited local and systemic AEs with QIVc vaccine in Study V130_12 (in subjects 2 to < 18 years of age) were generally similar to those reported in study V130_03 (4 to < 18 years of age). Nevertheless, some differences were observed, especially in the solicited local AEs, in which fewer events were reported in study V130_12 than in the previous V130_03 study.

The most commonly reported solicited local AEs were erythema, pain and tenderness. The majority were mild to moderate in severity and the most commonly reported solicited systemic AEs were headache, feeling fatigue or tiredness and the majority were mild to moderate in severity. Fever ($\geq 38^{o}$ C) was reported by 5.3% and 4.5% in QIVc and comparator group, respectively.

In addition, no SAEs, NOCD and deaths in paediatric and adult populations were judged by the investigator as possibly/ probably related to TIVc and QIVc in all studies reported.

Post marketing experience of TIVc, prior to discontinuation of the product, indicated that no new safety signals were identified. In the same line, postmarketing experience with QIVc (since it was approved) has not identified any safety concerns.

3.5. Uncertainties and limitations about unfavourable effects

Flucelvax (TIVc) is expected to have the same safety profile as the authorized Flucelvax tetra (QIVc) according to the data submitted for the MA of Flucelvax tetra in subjects ≥9 years of age. However, in the initial MA, the applicant submitted safety data from subjects aged 4 years of age and older with TIVc and QIVc, being both vaccine were well tolerate, with a good and similar safety profile.

There are no data available for TIVc in subjects aged 2-4 years. However, QIVc was well tolerated, with good reactogenicity and safety profile in subject aged 2-18 years. Therefore, it would be expected that the TIVc vaccine will present a similar safety profile than QIVc in this cohort.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

In Europe, each year, seasonal influenza is responsible for up to 50 million symptomatic cases in the European Union/European Economic Area (EU/EEA), and 15 000–70 000 European citizens die of causes associated with influenza.

Efficacy of Flucelvax in subjects from 2 years of age is demonstrated by clinical studies with the previously authorized similar trivalent vaccine and with the equivalent tetravalent vaccine. Efficacy is also supported by more than 15 studies showing that the vaccine is immunogenic both in its trivalent and tetravalent form.

As with any influenza vaccines, the efficacy varies according to the matching of the circulating strains with the vaccine strains. Efficacy may also vary according to the virulence of the strain and the affected population, including the age.

3.6.2. Balance of benefits and risks

The benefit/risk balance for Flucelvax is considered positive and supports the use of the vaccine for prophylaxis of influenza in adults and children from 2 years of age.

3.7. Conclusions

The overall benefit/risk balance of Flucelvax is positive, subject to the conditions stated in section 'Recommendations'.

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 is favourable in the following indication(s):

Prophylaxis of influenza in adults and children from 2 years of age.

Flucelvax 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.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.