27 March 2025
EMA/122377/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Flucelvax

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

Procedure No. EMEA/H/C/006532/II/0001

Note

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

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List of abbreviations

aVE	absolute vaccine efficacy
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CSR	Clinical Study Report
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HI	hemagglutination inhibition
ICH	International Conference on Harmonisation
ILI	influenza-like illness
LL	lower limit
MDCK	Madin-Darby Canine Kidney
MenC	meningococcal group C polysaccharide conjugate vaccine
MN	microneutralization
N/A	not applicable
NA	neuraminidase
NH	Northern Hemisphere
NP	nasopharyngeal
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update Report
QIV	quadrivalent influenza vaccine
QIVc	cell-based quadrivalent subunit influenza virus vaccine
RT-PCR	reverse transcription-polymerase chain reaction
SAP	Statistical Analysis Plan
SCR	seroconversion rate
SH	Southern Hemisphere
TIVc	cell-based trivalent subunit influenza virus vaccine
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Seqirus Netherlands B.V. submitted to the European Medicines Agency on 3 December 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of children from 6 months of age and older for FLUCELVAX, based on results from study V130_14. This is a Phase III, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine When Administrated in Healthy Subjects Aged 6 Months Through 47 Months. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.0 of the RMP is also being submitted.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the MAH took the opportunity to implement changes to sections 4.4 and 4.5 of the SmPC.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision 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.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Sol Ruiz

Timetable	Actual dates
Submission date	3 December 2024
Start of procedure	28 December 2024
CHMP Rapporteur Assessment Report	21 February 2025
PRAC Rapporteur Assessment Report	26 February 2025
PRAC members comments	05 March 2025
Updated PRAC Rapporteur Assessment Report	05 March 2025
PRAC Outcome	13 March 2025
CHMP members comments	17 March 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 March 2025
CHMP Opinion	27 March 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

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

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

State the claimed the therapeutic indication

Prophylaxis of influenza in adults and children from 6 months of age.

Epidemiology, risk factors and prevention

Influenza is a highly contagious infectious disease of global importance, with seasonal epidemics occurring predominantly during the winter months in the Northern and Southern Hemispheres. Annual vaccination is currently the most effective way to prevent influenza. Children <5 years of age, and particularly those <2 years of age, are at high risk of infection and of developing severe influenza and serious influenza-related complications (Izurieta et al. 2000; Bourgeois et al. 2006). An estimated 109.5 million influenza virus episodes were reported globally in 2018 in children <5 years of age, accompanied by an estimated 870,000 influenza-associated hospital admissions and 34,800 influenza-associated deaths (Wang et al. 2020). Young children are therefore a priority group for annual seasonal influenza vaccination throughout the world (WHO 2012; AAP 2016). Vaccination of children against influenza may also reduce community viral transmission (Mertz et al. 2016).

For many years, seasonal influenza vaccines were trivalent influenza vaccines (TIVs) composed of antigens from 3 influenza strains: 2 influenza A strains (A/H1N1 and A/H3N2) and 1 influenza B strain (either B/Yamagata or B/Victoria). The inclusion of only 1 B strain in TIVs has resulted in a risk of mismatch between the vaccine and the circulating influenza B strain (Peltola, Ziegler, and Ruuskanen 2003; Hu et al. 2004). Avoiding this risk of mismatch has been especially important in children as influenza B infections are reported to occur more often in children than in adults and are associated with a higher risk of complications and mortality in children (Belshe 2010; Ambrose and Levin 2012). Quadrivalent influenza vaccines (QIVs) containing B strains from both lineages were therefore developed to give broader protection against circulating influenza 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).

Aetiology and pathogenesis

Influenza is a highly contagious infectious disease that occurs in epidemics throughout the winter months. 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 HA and 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 influenza virus strain is no longer in circulation since September 2023.

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.

2.1.2. About the product

Flucelvax is a trivalent surface antigen, inactivated, influenza vaccine, prepared in Madin-Darby Canine Kidney (MDCK) cell cultures. The active substance comprises virus surface antigens (hemagglutinin [HA] and neuraminidase [NA]) of the 3 strains of influenza virus recommended by the World Health Organization (WHO) for the Northern or Southern Hemisphere season:

- 2 A strains (H1N1 and H3N2)
- 1 B strain (Victoria lineage)

The manufacturing process and formulation of TIVc (Cell-derived trivalent subunit influenza virus vaccine Flucelvax) and QIVc (Flucelvax Tetra in Europe and Flucelvax Quadrivalent in the United States [US]) are the same, with the exception of an additional B strain included in QIVc. Therefore, clinical study experience with QIVc provides valuable data for assessment of the overall efficacy, immunogenicity and safety of TIVc.

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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Study V130_14 (NCT03932682, EudraCT number 2018-001857-29), a Phase 3 efficacy, immunogenicity, and safety study of cell-based quadrivalent influenza vaccine (QIVc) in children 6 months through 47 months of age. This study is part of a Paediatric Investigation Plan (PIP) agreed by the EMA Paediatric Committee (PDCO).

This study was initiated in May 2019. Study completion was delayed until 2024 due to the impact of the COVID-19 pandemic on the management of clinical trials and on the significant reduction in global influenza activity for the first 2 years of the pandemic. During this time, the B/Yamagata influenza virus strain was confirmed to no longer be in circulation, and thus in September 2023, the WHO recommended a transition from quadrivalent influenza vaccines to trivalent influenza vaccines for seasonal influenza prophylaxis.

The design of the study is consistent with the EMA Guideline on Influenza Vaccines Non-clinical and Clinical Modules (EMA/CHMP/VWP/457259/2014) and the CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (CBER 2007).

Study V130_14 was designed in consultation with the relevant regulatory agencies. Following regulatory feedback that all subjects were to receive some benefit from participating in the study, the option of placebo only as the comparator vaccine was omitted. Therefore, all subjects in the comparator group, including those enrolled in countries without a NeisVac-C (Pfizer Limited) marketing authorisation, were to receive Neisseria meningitidis serogroup C polysaccharide conjugate vaccine (MenC vaccine) as active immunisation to prevent meningitis or septicaemia caused by Neisseria meningitidis serogroup C. For those subjects scheduled to receive 2 doses of study vaccine, a saline placebo was used to maintain the study blind. In the countries without a NeisVac-C marketing authorisation, additional safety information was collected for 28 days after MenC vaccination at Visit 5 for the subjects who were aged 6 months through 11 months at enrolment.

2.1.4. General comments on compliance with GCP

Study V130_14 was designed, implemented, and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, ICH E6(R2), and Japanese Ministry of Health, Labor, and Welfare, Seqirus codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (ICH 2016; FDA 1997; European Parliament Council 2001).

The study was conducted in compliance with the protocol, GCP, and applicable regulatory requirements.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

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

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is acceptable.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of TIVc (Flucelvax).

2.3. Clinical aspects

2.3.1. Introduction

The manufacturing process and formulation of TIVc (Cell-derived trivalent subunit influenza virus vaccine Flucelvax) and QIVc (Flucelvax Tetra in Europe and Flucelvax Quadrivalent in the United States [US]) are the same, with the exception of an additional B strain included in QIVc. Therefore, clinical study experience with QIVc provides valuable data for assessment of the overall efficacy, immunogenicity and safety of TIVc.

The QIVc clinical development program includes studies designed to support an indication of active immunization against influenza caused by the type A and type B influenza viruses present in the QIVc vaccine in persons aged 6 months and older. The previous development of TIVc was the foundation of development of the quadrivalent version of Flucelvax.

The initial QIVc regulatory submission included data from 2 QIVc Phase 3 noninferiority immunogenicity and safety clinical studies: 1 study in adults aged 18 years and older (Study V130_01, NCT01992094) and 1 study in children 4 to <18 years of age (Study V130_03, NCT01992107, EudraCT number 2015-000133-70). The registration for QIVc was supported by 12 randomized controlled studies of TIVc in adults and in children aged 3 years and older.

Based on the initial clinical data, QIVc was approved by the US Food and Drug Administration (FDA) in May 2016 (tradename Flucelvax Quadrivalent) for the prevention of influenza in adults and children aged 4 years and older under an accelerated approval pathway. QIVc was approved for use in adults and children aged 9 years and older by the European Medicines Agency (EMA) in December 2018 (tradename Flucelvax Tetra), and also approved in Canada in November 2019 and in Australia in August 2020.

The third clinical study completed for QIVc, Study V130_12 (NCT03165617, EudraCT number 2016-002883-15), was a Phase 3/4 efficacy, immunogenicity, and safety study in children 2 to <18 years of age. This study was conducted to meet the United States (US) post-marketing requirement to confirm the clinical benefit of QIVc for use in children aged 4 years and older. In Europe, the European Commission (EC) granted an age extension to 2 years and older in October 2020 and in the US, the FDA granted an age extension to 2 years and older, approved in March 2021.

The fourth clinical study completed for QIVc, Study V130_10 (NCT04074928, EudraCT number 2020-002785-13), was a Phase 3 efficacy, immunogenicity, and safety study in children 6 months through 47 months of age. This study was conducted to fulfill the US FDA deferred paediatric study requirement for QIVc under the Pediatric Research Equity Act (PREA). In the US, the FDA granted a further age extension to 6 months and older, approved in October 2021. QIVc is authorised for use in adults and children from 6 months of age and older in Argentina (November 2021), Canada (March 2022), Taiwan (June 2022), Australia (July 2023), New Zealand (July 2023), and Great Britain (October 2023) and the EU (December 2024).

The current addendum provides information on the fifth clinical study completed for QIVc, Study V130_14 (NCT03932682, EudraCT number 2018-001857-29), a Phase 3 efficacy, immunogenicity, and safety study in children 6 months through 47 months of age. This study is part of a PIP agreed by the

EMA Paediatric Committee (PDCO). A positive opinion for the extension of the indication from 6 months of age and older was granted for QIVc on 12 December 2024.

Study V130_14 was designed in consultation with the relevant regulatory agencies. Following regulatory feedback that all subjects were to receive some benefit from participating in the study, the option of placebo only as the comparator vaccine was omitted. Therefore, all subjects in the comparator group, including those enrolled in countries without a NeisVac-C (Pfizer Limited) marketing authorization, were to receive Neisseria meningitidis serogroup C polysaccharide conjugate vaccine (MenC vaccine) as active immunization to prevent meningitis or septicaemia caused by Neisseria meningitidis serogroup C. For those subjects scheduled to receive 2 doses of study vaccine, a saline placebo was used to maintain the study blind. In the countries without a NeisVac-C marketing authorisation, additional safety information was collected for 28 days after MenC vaccination at Visit 5 for the subjects who were aged 6 months through 11 months at enrolment.

GCP

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

The MAH 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 Overview of QIVc V130_14 Clinical Study Design

Study No. **Countries (No. of Sites)** **Influenza Seasons**	**Study Design** **(Comparator)** **[assay used for efficacy and immunogenicity objectives]**	**No. of Subjects Enrolled / Completed Protocol**	**Characteristic and Age of Subjects**	**Vaccination Schedule (IM doses)**	**Objectives**
V130_14 Bangladesh (1), Bulgaria (7), Czech Republic (5), Estonia (7), Honduras (3), Latvia (1), Malaysia (5), New Zealand (2), Pakistan (5), Philippines (12), Poland (8), Romania (4), South Africa (9), Thailand (3), Ukraine (3) SH 2019 NH 2019/2020 NH 2020/2021 NH 2022/2023 SH 2023	Phase 3, randomized, comparator-controlled, observer-blind study (Non-influenza vaccine comparator: meningococcal group C polysaccharide conjugate vaccine [MenC; NeisVac-C]) [RT-PCR and culture confirmed assays for efficacy objectives; HI and MN assays for immunogenicity objectives]	QIVc: 2860/2794 MenC: 2863/2766	Healthy children 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 MenC: Previously vaccinated: 1 vaccination of 0.5 mL Not previously vaccinated: 1 vaccination of 0.5 mL plus 1 vaccination of placebo (saline for injection)	Efficacy Immunogenicity Safety

Source: Section 5.3.5.1, V130_14 CSR.

Abbreviations: HI = hemagglutination inhibition; IM = intramuscular; MenC = meningococcal group C polysaccharide conjugate vaccine; MN = microneutralization; NH = Northern Hemisphere; No. = number; QIVc = cell-based quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription-polymerase chain reaction; SH = Southern Hemisphere.

2.3.2. Pharmacokinetics

No clinical pharmacology or pharmacokinetic studies were performed in the clinical development program of TIVc because the pharmacokinetic properties of influenza vaccines do not provide useful information for establishing adequate dosing recommendations.

2.3.3. Pharmacodynamics

Mechanism of action

TIVc 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 haemagglutinin proteins. These antibodies neutralise influenza viruses.

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

Assays Supporting the Immunogenicity Assessments in Study V130_14

In Study V130_14, immunogenicity endpoints were assessed by the HI and enzyme-linked immunosorbent assay (ELISA)-based microneutralization (MN) assay for all strains. Serum samples were collected before vaccination on Day 1 and on Day 29 (previously vaccinated subjects receiving a single vaccine dose) or Day 57 (not previously vaccinated subjects receiving 2 doses). Serum samples were tested at a central laboratory (VisMederi srl, Siena, Italy).

The HI and MN assays were performed on serum samples collected each season from a subset of enrolled subjects. The HI assay method was used to measure influenza-specific serum antibody levels to each vaccine strain in accordance with the EMA Guideline on Influenza Vaccines Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014). The MN assay was also performed and considered the primary immunogenicity assessment for the A/H3N2 strains due to recent evolutionary changes in the amino acids of the surface proteins hemagglutinin (HA) and neuraminidase (NA) of A/H3N2 viruses, resulting in a diminished capacity of HA to agglutinate target red blood cells in the HI assay, or agglutination has been shown to be mediated by NA in the HI assay (Mögling et al. 2017).

2.3.4. Discussion on clinical pharmacology

The haemagglutination inhibition (HI) assay used for immunogenicity evaluation of influenza vaccines is considered adequate for the V130_14 QIVc study and therefore, for the TIVc, because it is in line with the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014). The MAH states that for the A/H3N2 strain, the primary immunogenicity assay was the MN assay as the HI assay was not performed if pre-validation activities determined there was a lack of agglutination of the red blood cells in the HI assay. 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 SH 2019 (A/North Carolina/04/2016) and Season NH 2020/2021 (A/Delaware/39/2019) and thus the use of MN assay is considered adequate.

It should be mentioned that HI and MN titres are not a true surrogate marker in the sense that there is not a globally accepted cut-off titre that defines clinical protection. Nonetheless, it has been widely shown that higher titres tend to correlate with better protection.

The MAH states that all sera were tested in a single clinical serology laboratory in line with the recommendations of the current CHMP influenza vaccines guideline, this is adequate.

Validation reports of the HI test were included in the variation application, corresponding to the different strains analysed in the different seasons of the study. All validations were carried out according to the EMA "Guideline on bioanalytical method validation", FDA "Guidance for Industry; Q2B Validation on Analytical Procedures Methodology", and ICH guidelines "Validation of analytical procedures: text and methodology; ICH Harmonised Tripartite Guideline, Q2(R1)". The parameters assessed were limit of quantitation and range, dilutional linearity, relative accuracy, precision-Intermediate precision, precision-repeatability, format variability, robustness and specificity. All acceptance criteria defined in the analysis validation plan were well achieved, and therefore it is concluded that the HI test was well validated.

Additionally, MN tests were also validated and the reports are included in the application. All validations were carried out according to the EMA "Guideline on bioanalytical method validation", FDA "Guidance for Industry; Q2B Validation on Analytical Procedures Methodology", and ICH guidelines "Validation of analytical procedures: text and methodology; ICH Harmonised Tripartite Guideline, Q2(RI)". The parameters assessed were limit of quantitation and range, dilutional linearity, relative accuracy, precision-Intermediate precision, precision-repeatability, format variability, robustness and specificity. All acceptance criteria defined in the analysis validation plan were well achieved, and therefore it is concluded that the MN test was well validated.

In light of the technical challenges with the HI assay, quantification of neutralizing antibody titres using the MN assay against Type A/H3N2 has been used as an alternative and is considered adequate.

2.3.5. Conclusions on clinical pharmacology

The purpose of this submission is to support the use of cell-derived trivalent influenza vaccine (TIVc) for persons aged 6 months and older based on additional data from the V130_14 study. TIVc was granted marketing authorization for use in persons 2 years and older on 15 November 2024 based on evidence from the clinical development of TIVc and QIVc.

The data submitted in this application from study V130_14 have been generated with QIVc, but it is relevant to TIVc because both vaccines are manufactured using the same process and have overlapping compositions.

No clinical pharmacology or pharmacokinetic studies were performed in the clinical development program of Flucelvax Tetra as the pharmacokinetic properties of influenza vaccines do not provide useful information for establishing adequate dosing recommendations (EMEA/CHMP/VWP/164653/2005).

The haemagglutination inhibition (HI) assay used for immunogenicity evaluation of influenza vaccines is considered adequate for the V130_14 QIVc study, because it is in line with the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014).

In light of the technical challenges with the HI assay, particularly with the A/H3N2 strain used in the vaccine in Season SH 2019 and NH 2020/2021, quantification of neutralizing antibody titres using the MN assay against Type A/H3N2 has been used as an alternative. The explanation of the observed problem and the solution implemented by the MAH are satisfactory.

Therefore, it is considered that all aspects dealing with clinical pharmacology in the QIVc have been well addressed and are relevant to TIVc, which is the aim of this extension of indication.

2.4. Clinical efficacy

2.4.1. Dose response studies

The dose-finding studies were conducted for the initial submission for QIVc. No dose-finding studies were conducted since the vaccine composition and dosing are based on the Guideline on Influenza vaccines – Quality module (EMA/CHMP/BWP/310834/2012 Rev.1), and the vaccine compositions are in line with the antigen dose of other seasonal inactivated non-adjuvanted influenza vaccines. The CHMP agreed it was not needed to perform dose-response studies.

2.4.2. Main study

V130_14

Title of Study

A Phase III, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine When Administrated in Healthy Subjects Aged 6 Months Through 47 Months.

Methods

This study was conducted over 5 influenza seasons at 75 centers in 15 countries. The study was performed during the Southern Hemisphere (SH) 2019, Northern Hemisphere (NH) 2019/2020, NH 2020/2021, NH 2022/2023, and SH 2023 influenza seasons.

Study V130_14 was conducted in accordance with the European Medicines Agency (EMA) Guideline on Influenza Vaccines: Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014) and the CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (CBER 2007). The study is part of a Paediatric Investigation Plan (PIP) agreed by the EMA Paediatric Committee (PDCO).

Efficacy Measurements

The case definition of influenza-like illness (ILI) for this study was the presence of a temperature ≥37.8°C (≥100.0°F) and at least one of the following symptoms on the same day: cough, sore throat, nasal congestion, rhinorrhoea, earache or ear discharge. These symptoms could have occurred at any time throughout the study and were to be reported immediately.

Subjects who met the protocol-defined ILI criteria had a nasopharyngeal (NP) swab collected at an unscheduled visit. The NP swab was targeted for collection within the first 24 hours or as soon as possible after ILI onset. ILI onset was defined as the first day that the subject met the protocol-defined ILI criteria. The end date was defined as the date the subject did not meet the criteria anymore, ie, the first day when the following conditions are met simultaneously: temperature <37.5°C (<99.5°F) with no fever reducers used, other symptoms (cough, sore throat, nasal congestion, rhinorrhoea, earache or ear discharge) either absent or mild, and a return of the child to normal activities. A new ILI episode would

only be considered after resolution of the previous one, as judged by the Investigator, with an interval of 14 days or more between the onset of the previous protocol-defined ILI and the onset of the new ILI episode.

Primary efficacy influenza events required the confirmation of influenza by RT-PCR testing of the NP swabs collected for ILI episodes during the surveillance period. In addition to RT-PCR testing, all swab samples were cultured for the propagation of the clinical strain of influenza obtained from the subject. If the result of RT-PCR testing was negative, culture activities were discontinued. For RT-PCR confirmed influenza samples, culturing activities continued, and cultures with ≥50% cytopathic effect (CPE) were harvested. Supernatants from these cultures underwent virus titration and those that met the viral threshold proceeded to be characterized as antigenically matched or unmatched to the vaccine strain using validated ferret antisera assays. If the primary laboratory was not able to sufficiently propagate the virus to allow for antigenic characterization, the sample was sent to a second laboratory to perform the intermediate culture step. Samples with a demonstrated CPE were shipped back to the primary laboratory to perform virus titration for antigenic characterization using the validated assays.

The case definition for moderate-to-severe ILI for this study was the presence of an ILI episode complicated by one of the following medically-attended AEs reported in the eCRF:

- Physician confirmed lower respiratory tract illness
- Physician confirmed acute otitis media
- Hospitalization in the Intensive Care Unit (ICU)
- Physician-diagnosed serious extra-pulmonary complication of influenza
- Supplemental oxygen requirement for more than 8 hours

Subjects with ILI symptoms and its complications were to be treated according to recent accepted (national) clinical standards.

Information on occurrences of any hospitalization, and administered or prescribed antibiotics or antivirals, was collected from the subject for the purposes of healthcare resource utilization assessment (regardless of whether or not the medical event, healthcare contact, or the use of medications were considered to be directly linked to the ILI). Analyses on these endpoints covered the period from ILI onset until 30 days after onset.

Both the case definition of ILI as well as the case definition for moderate-to-severe ILI are considered adequate.

Immunogenicity Measurements

The measures of immunogenicity used in this study were standard, ie, widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response). The measures were determined by the HI and/or MN assay by titrating antibodies against the influenza strains homologous to the seasonal influenza vaccine. The HI and MN tests were conducted on serum samples collected immediately before first vaccination and 28 days after last vaccination in the treatment period.

To further characterize the immune response, additional exploratory immunogenicity analyses may be conducted on the immunogenicity subset using other tests such as an anti-neuraminidase assay. In case of exploratory immunogenicity analyses, the immune response would be characterized in a similar manner.

Testing was conducted by Seqirus or a Seqirus designated (contracted) laboratory in a blinded manner towards the treatment arm. Laboratory data were transferred to an external CRO providing data analysis.

The management of the nasopharyngeal swabs, the RT-PCR confirmation and the cell culture activities for strain subtype determination are endorsed. The table that details the route of swab collection (Table 11-1 in the CSR) has three items: nasopharyngeal, oropharyngeal and other. The sum of the three percentages is not equal to 100%. The MAH explained that there were two reasons to explain why the sum of the percentages for nasopharyngeal, oropharyngeal, and other swab types was not equal to 100%. The first reason was that the percentages for each route of collection use the total N from the 'Collection of swab for ILIs reported >14 days after last vaccination to end of influenza season' and the second one was that a single influenza-like illness (ILI) could involve the collection of swabs from multiple routes.

The use of HI and MN assays to describe immunogenicity is according to the CHMP Guideline on influenza vaccines – Non-clinical and clinical module. The Cell Mediated Immunity (CMI) was not measured in this study because CMI response to QIVc vaccine in young children was previously evaluated in study V130_10.

Study participants

A total of 5723 subjects 6 months through 47 months of age were enrolled in the study (All Enrolled Set) and randomized in a 1:1 ratio to receive QIVc or the comparator vaccine. Of the 5723 randomized subjects, 26 subjects did not receive study vaccine. In total, 5697 subjects received at least one study vaccination (All Exposed Set).

The majority of subjects (97.2%) completed the study; 163 (2.8%) subjects discontinued from the study. The most common reasons for discontinuing from the study was withdrawal of consent (1.4%) followed by lost to follow up (0.8%).

Subject Characteristics and Main Criteria for Inclusion and Exclusion

Main Inclusion criteria

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

1. Individuals of 6 through 47 months of age on the day of informed consent.

2. Individuals in generally good health as per the Investigator's medical judgement.

Main 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 vaccination and blood draws.

4. A known history of Guillain-Barré Syndrome or other demyelinating diseases such as encephalomyelitis and transverse myelitis.

5. Abnormal function of the immune system resulting from clinical conditions, including:

6. Received immunoglobulins or any blood products within 180 days prior to informed consent.

7. Received influenza vaccination or had documented influenza disease in the last 6 months prior to informed consent.

8. Prior vaccination to prevent Neisseria meningitidis serogroup C disease or prior infection caused by this organism.

9. Received any other vaccines than influenza vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to study vaccination or was planning to receive any vaccine within 28 days after study vaccination.

Treatments

Subjects in the QIVc group received a 0.5 mL intramuscular (IM) dose of QIVc (1 or 2 doses, depending on influenza vaccination history). Subjects in the comparator vaccine group received a 0.5 mL IM dose of the non-influenza comparator vaccine (meningococcal group C polysaccharide conjugate vaccine; MenC vaccine). For subjects in the comparator vaccine group who were not previously vaccinated, the second dose of study vaccine during the treatment period was a 0.5 mL IM dose of saline for injection.

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). The strain composition of each of the formulations of QIVc used in this study (SH 2019, NH 2019/2020, NH 2020/2021, NH 2022/2023, and SH 2023) corresponds to the WHO recommended composition for each influenza season in the corresponding geographical area.

Meningococcal Group C Polysaccharide Conjugate Vaccine (MenC Vaccine)

MenC vaccine (NeisVac-C, Pfizer Limited) is a Neisseria meningitidis serogroup C polysaccharide conjugate vaccine.

The total number of study participants is considered appropriate to demonstrate absolute vaccine efficacy.

The inclusion/exclusion criteria are considered satisfactory.

Moreover, the strain composition of the vaccine met the WHO and CHMP recommendations for the seasons in which the CT were performed.

Objectives

Primary Efficacy Objective:

The primary efficacy objective was to demonstrate the absolute vaccine efficacy of QIVc versus a comparator to prevent at least one of the following:

a) RT-PCR confirmed illness caused by any influenza Type A and/or Type B virus, regardless of antigenic match.

b) Culture confirmed illness caused by influenza virus strains antigenically matched to the influenza strains selected for the seasonal influenza vaccine.

Secondary Efficacy Objectives:

The secondary efficacy objectives evaluated QIVc compared to a non-influenza vaccine, as follows:

- Prevention of culture confirmed illness caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine.
- Prevention of culture confirmed illness caused by any Type A and/or Type B virus.
- Prevention of RT-PCR confirmed moderate-to-severe illness caused by any influenza Type A and/or Type B virus.

Secondary Immunogenicity Objective:

The secondary immunogenicity objective was to evaluate the immune response after vaccination with QIVc, 4 weeks after last vaccination in a subset of subjects 6 months through 47 months of age in each study vaccine group.

Exploratory Objectives:

The exploratory objectives were:

- To characterize the immune response by other assays.
- To use genotypic methods to characterize circulating strains of influenza collected during the study.

Outcomes/endpoints

Primary Efficacy Endpoints:

The primary endpoints evaluated QIVc compared to a non-influenza vaccine, as follows:

a) First occurrence of RT-PCR confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.

b) First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints evaluated QIVc compared to a non-influenza vaccine, as follows:

- First occurrence of culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.
- First occurrence of culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.
- First occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season.

Secondary Immunogenicity Endpoints:

The measures for immunogenicity were determined by HI and MN assay, as applicable, prior to vaccination (Visit 1) and 28 days after last vaccination for each of the four influenza strains. For each

assay the measures included:

- Pre- and postvaccination geometric mean titers (GMTs).
- Seroconversion rate (SCR): Defined as the percentage of subjects with either a prevaccination HI (or MN) titer <1:10 and a postvaccination HI (or MN) titer ≥1:40, or a prevaccination HI (or MN) titer ≥1:10 and a ≥4-fold increase in postvaccination HI (or MN) titer.
- Geometric mean ratio (GMR): Defined as the geometric mean of the fold increase of postvaccination HI (or MN) titer over the prevaccination HI (or MN) titer.

Exploratory endpoints

As stated in the CSR for study V130_14, exploratory objectives were not analysed.

All objectives are considered acceptable. Particularly, it is important to note that the primary endpoint is aimed at demonstrating clinical efficacy in terms of disease prevention.

The primary objective is made of two parts, and the objective would be met if at least one of the two parts is achieved. One of the parts is to demonstrate efficacy of QIVc against RT-PCR confirmed ILI cases regardless of antigenic match and the other to demonstrate vaccine efficacy against culture confirmed illness caused by influenza virus strains antigenically matched to the vaccine composition. This approach is found to be sensible. An estimation of efficacy against influenza due to strains that are well-matched or unmatched (RT-PCR or culture confirmed) to those in the vaccine was analysed. This is considered important to show the overall potential benefit of the vaccine.

The secondary efficacy objectives are agreed upon, especially the prevention of culture confirmed illness caused by any influenza type A and/or type B virus and the prevention of RT-PCR confirmed moderate-to-severe illness caused by any influenza type A and/or type B virus.

The third secondary objective, the prevention of culture conformed illness caused by influenza virus strains antigenically dissimilar to the vaccine composition, has been evaluated for completeness and as a way of complementing the information on VE coming from the antigenically matched strains.

The efficacy endpoint definitions followed the EU guidance, so they are considered adequate. An ILI case was defined as body temperature of ≥100.0°F/ ≥37.8°C (i.e., fever) along with any of the following symptoms: cough, sore throat, nasal congestion, rhinorrhoea, earache or ear discharge. This ILI definition goes along with the guideline on Influenza vaccines (EMA/CHMP/VWP/457259/2014) recommendations and take into account the ECDC European Centre for Disease Prevention and Control (ECDC) definitions for ILI. The Influenza case definition was also properly defined following also the EU recommendations.

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 on the number of RT-PCR confirmed influenza cases and the number of culture confirmed influenza cases, so the sample size estimate was only for operational reasons (an estimate of number of subjects needed to assess the endpoint).

For the primary efficacy endpoint 1a, assuming an attack rate in the comparator group of 8% and an influenza VE of 40%, an estimated sample size of minimally 2,974 evaluable subjects (or 1,487 evaluable subjects per study group) with a minimum total of 191 cases would be needed to have at least 90% power to reject the null hypothesis that the VE is less or equal to 0% at the significance level alpha=0.0125 and the risk of infection contained entirely within period covered by follow-up. For the primary efficacy endpoint for vaccine antigenically matched strains (1b), assuming an attack rate in the

comparator groups of 4%, a VE of 50%, α=0.0125, a minimum of 3,446 evaluable subjects and a minimum number of 104 cases would be needed to have at least 90% power to reject the null hypothesis that the VE is less or equal to 0% at the significance level alpha= 0.0125. These results assumed that the HR was constant throughout the study and that Cox proportional hazard regression was used for the analysis. Table 2 summarizes the power calculations assumptions and the number of cases required to meet primary efficacy endpoints.

Table 2 Power calculation of multiple primary endpoints

Primary Objective	VE Success Criteria	Assumed VE	Alpha (α)	Influenza attack rate in comparator group	Power	Approximate evaluable subjects per treatment group	Approximate total subjects enrolled	Minimum number of ILIs to demonstrate LL 2-sided 97.5% CI for VE is > 0%
1a	0%	40%	0.0125	8%	>90%	1487	3306	191
1b	0%	50%	0.0125	4%	>90%	1723	3830	104

Abbreviations: CI = confidence interval; ILI = influenza-like illness; LL = lower limit; VE = vaccine efficacy.

Accounting for 10% early dropout and uncertainty about the assumed parameters, an approximate number of 3830 subjects were planned to be enrolled (or 1915 subjects per study group) to demonstrate that the LL of the two-sided 97.5% CI for the VE was greater than 0% for the primary endpoint assessment.

The study was designed to accrue a minimum of 191 RT-PCR confirmed influenza cases and a minimum of 104 culture confirmed influenza cases antigenically matched to the strains selected for the seasonal vaccine. If the overall/pooled influenza attack rate differed from the predicted rate and/or influenza strain circulation within a study season drifted or shifted away from the strains selected for the seasonal vaccine, an adjustment of the prospectively specified number of cases, and number of subjects would be required. Extraneous real-life information, from (but not limited to) the influenza surveillance systems of the ECDC, US CDC, or WHO could be used to re-assess the influenza event rate.

Sample Size for Secondary Immunogenicity Objectives (Immunogenicity Subset)

Per season, with a 1:1 allocation, approximately 100 evaluable subjects from the active arm and 100 evaluable subjects from the comparator arm were to be enrolled into the immunogenicity subset. Assuming a 10% drop-out rate, approximately 222 subjects were allocated to the immunogenicity subset per influenza season.

Randomisation

Subjects were randomized in a 1:1 ratio to receive QIVc or the non-influenza vaccine comparator (meningococcal group C polysaccharide conjugate vaccine [MenC vaccine]; NeisVac-C). Randomization was stratified by age, with a planned distribution of at least 30% of subjects aged 6 months through 23 months and at least 30% of subjects aged 24 months through 47 months. Enrolled subjects were also stratified by influenza vaccination history ("previously vaccinated" and "not previously vaccinated") to allow for assignment of the appropriate number of doses of study vaccine. Previously vaccinated subjects were scheduled to receive a single dose of 0.5 mL of the study vaccine (QIVc or MenC) on Day 1. Not previously vaccinated subjects were scheduled to receive 2 doses of 0.5 mL of the study vaccine (QIVc/QIVc or MenC/placebo), administered 28 days apart, on Day 1 and Day 29.

The study protocol allowed for analyses of interim data for early evidence of efficacy to enable early study termination when a statistically robust demonstration of efficacy is observed.

Blinding

This trial was designed as an observer-blind study.

Statistical methods

Analysis sets

All Enrolled Set

All screened subjects who provided informed consent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a Subject ID.

All Exposed Set

All subjects in the All Enrolled Set who received a study vaccination.

Full Analysis Set (FAS) Efficacy

As defined in the final SAP (Version 2.0, dated 07 September 2021), the FAS Efficacy consisted of all subjects in the All Enrolled Set who were randomized, received at least one dose of study vaccination, and were evaluated for efficacy at more than 14 days after the last vaccination.

FAS Immunogenicity

As defined in the final SAP (Version 2.0, dated 07 September 2021), the FAS Immunogenicity consisted of all subjects in the All Enrolled Set who were randomized, received at least one study vaccination, and provided evaluable serum samples at both baseline (Day 1) and 28 days after last vaccination (Day 29/57).

In case of vaccination error, subjects in the FAS Efficacy and FAS Immunogenicity were analyzed "as randomized" (ie, according to the study vaccine a subject was designated to receive, which may be different from the study vaccine the subject actually received).

If a subject was unblinded during the study, he/she was included in the FAS.

PPS Efficacy/Immunogenicity

All subjects in the FAS Efficacy/Immunogenicity who:

- Correctly received the study vaccine (ie, received the study vaccine to which the subject was randomized and at the scheduled time points).
- Had no protocol deviations leading to exclusion as defined prior to unblinding/analysis.
- Were not excluded due to other reasons defined prior to unblinding or analysis

The PPS is a subset of the FAS and was always defined even if the objectives did not require it.

Subgroup Analysis

Subgroup analyses were performed for vaccine efficacy by stratifying for the following subgroups:

- Subjects aged "6 through 23 months" and "24 through 47 months"
- Subjects "previously influenza vaccinated" and "not previously influenza vaccinated"
- Subjects by race
- Subjects by sex

- Subjects by country or region
- Subjects by season/year treated

Additional immunogenicity analyses were performed for each season by stratifying for the following subgroups:

- Subjects aged "6 through 23 months" and "24 through 47 months"
- Subjects with prevaccination HI (or MN) titer <1:10 and prevaccination HI (or MN) titer ≥1:10
- Subjects "previously influenza vaccinated" and "not previously influenza vaccinated"
- Subjects by race
- Subjects by sex
- Subjects by country or region

Efficacy Analysis

The primary efficacy analysis was based on the FAS Efficacy. Absolute vaccine efficacy was only assessed for RT-PCR confirmed influenza episodes (primary efficacy objective 1a) and culture confirmed influenza episodes antigenically matched to the strains selected for the seasonal vaccine (primary efficacy objective 1b) with first onset of illness occurring at >14 days after the last vaccination in the treatment period (since clinical protection is not immediate after vaccination) until the end of the influenza season. Additionally, the primary objective was evaluated in PPS Efficacy.

Time-to-event methodology based on a proportional hazard model was used for all efficacy analyses to estimate the hazard ratio (HR). Absolute vaccine efficacy (aVE) against first occurrence RT-PCR confirmed influenza cases was determined using a standard formula: aVE = 1 − HR where HR is the hazard ratio for RT-PCR influenza confirmed cases in the QIVc group versus the 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 ≤ 0 versus H1: 1 − HR > 0

where HR is a hazard ratio of QIVc versus the comparator vaccine and VE is vaccine efficacy.

For both primary efficacy objectives, the HR and the related 97.5% CI of HR for onset of first RT-PCR confirmed influenza were estimated by a proportional hazards regression model with treatment effect as a fixed effect and stratifying covariates as random effect:

$hi(t|X) = h0(t) \exp(\beta TX + bTZ)$

with t denoting time to the influenza, β is the effect of treatment group indicated by X, b is random effect (assumed as a multivariable random gaussian variable with zero mean and diagonal covariance matrix), Z is random effect covariate (reflecting randomization strata).

Subjects who did not experience an event during the observation period and subjects who dropped out from the study during the observational period were censored (right-censoring) at the last available date in the eCRF prior to the end of influenza season.

The estimate of the HR, the respective estimate for absolute VE and the pertaining two-sided Cis were calculated based on this model, including treatment group (2 treatments), age strata (2 categories, 6 months through 23 months or 24 months through 47 months), gender (male or female), vaccination history (yes or no), country, and investigator site (site identifier).

If the study continued over several seasons, estimates would also be adjusted for the factor season(s). In case of one or two (interim) analyses, confidence levels at each stage would be adjusted to provide 97.5% overall coverage.

For each of the multiple primary objectives, estimates for the HR in the Cox Proportional Hazard model were calculated using the Maximum Likelihood (ML) method. In case of problems with convergence (algorithm does not converge or converges to infinite estimates), the penalized ML approach would be used (Heinze and Schemper 2001).

Success Criteria for the Multiple Primary Efficacy Objectives

The primary objective of efficacy was achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints, that is, if the lower limit (LL) of the two-sided 97.5% CI of VE was greater than 0% in subjects 6 months through 47 months of age.

In the case that an interim analysis was performed, the 97.5% CI would be adjusted accordingly. If an interim analysis was performed and the trial continued, then all the subsequent analysis would be tested at a reduced alpha level, ie, what was left from the interim analysis.

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

Secondary efficacy objectives were not associated with any hypothesis testing.

Immunogenicity Analysis

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

Crude estimates for GMTs, GMRs, and pertaining two-sided 95% CIs were calculated assuming log-normal distribution of the titers and were completed by providing minimum, maximum, and median titers for each vaccine group.

To determine the adjusted GMTs and associated two-sided 95% CI, a general linear model was fitted on log-transformed (base 10) post-GMT titers as the outcome variable and with covariates such as vaccine group, log10-transformed prevaccination titer, age group, previous vaccination status, sex, and investigator site. From the model, the adjusted GMT and their confidence intervals, were produced with 95% confidence limits. The adjusted baseline GMTs were calculated in a similar fashion without adjusting for log10-transformed prevaccination titer as a covariate.

The analysis model for the fold increase (GMRs) in titers was performed using the same model as mentioned; however, using the log-transformed (base 10) post-GMT minus the log-transformed (base 10) pre-GMT as the outcome variable and excluding log-transformed (base 10) prevaccination titer as a covariate. The adjusted GMR and 95% CI were calculated by taking the anti-logs of the means and 95% CI of the log transformed fold increases in postvaccination titer over prevaccination titers.

Binary data (ie, percentages of subjects with seroconversion and with titer ≥1:40) were summarized for each vaccine group using crude estimates and were reported together with two-sided 95% CIs calculated according to Clopper's and Pearson's (1934) method. No multiplicity adjustment to the CI levels was implemented.

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

No statistical testing was performed for the comparative secondary immunogenicity objectives.

Interim Analysis

As the circulation of influenza viruses is seasonal and the event rates of influenza are difficult to predict, this study had a group sequential design in order to allow analyses of interim data to enable early study termination when a statistically robust demonstration of efficacy was observed.

One interim analysis for early evidence of efficacy was conducted in accordance with the protocol after the completion of 3 seasons of the study, and the DMC recommendation was for the study to continue. Based on the result of the interim analysis, the CIs for the primary efficacy endpoints were adjusted and the sample size of the enrolled population was increased to accrue the cases required for the final analyses.

The sample size calculations in order to have at least 90% power to demonstrate QIVc vaccine efficacy are considered adequate.

Subjects were randomized in a 1:1 ratio to receive QIVc or the non-influenza vaccine comparator (meningococcal group C polysaccharide conjugate vaccine [MenC vaccine]; NeisVac-C). Randomisation was stratified by age (6 through 23 months and 24 through 47 months) and by influenza vaccination history. Both types of stratification are sensible taking into account the study population, which is composed of very young children that will most likely present diverse immune responses determined by their age and also influenced by whether they have been previously vaccinated against influenza. It was determined that at least 30% of the participants had to be in each of the two age groups, this is acknowledged and agreed.

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 and therefore acceptable.

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.

The statistical methods are overall considered adequate. In study V130_14 the primary objective of efficacy was achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints, that is, if the lower limit (LL) of the two-sided 97.5% CI of VE was greater than 0% in subjects 6 months through 47 months of age. 0% is very low having in mind that for instance, in study V130_12, which supported the extension of indication from 9 years and above to 2 years and above, as well as in supporting clinical studies for other authorised flu vaccines in children aged from 6 to 35 months, the LL of the 2-sided CI of the VE estimate, with at least 95% coverage was higher than 20%. The MAH indicated that study V130_14 started before the results of study V130_12 were known (in which the LL of the CI for aVE was >20% for subjects 2 to <18 years); that study V130_14 had majority of subjects that were not previously vaccinated and were below 2 years of age, so the response of the children in study V130_14 was expected to be lower than in study V130_12; and that the lower bound of the VE for study V130_14 was agreed by the PDCO and also supported by interactions with regulatory agencies. Therefore, the LL for the CI of the VE criterion is considered sufficiently justified.

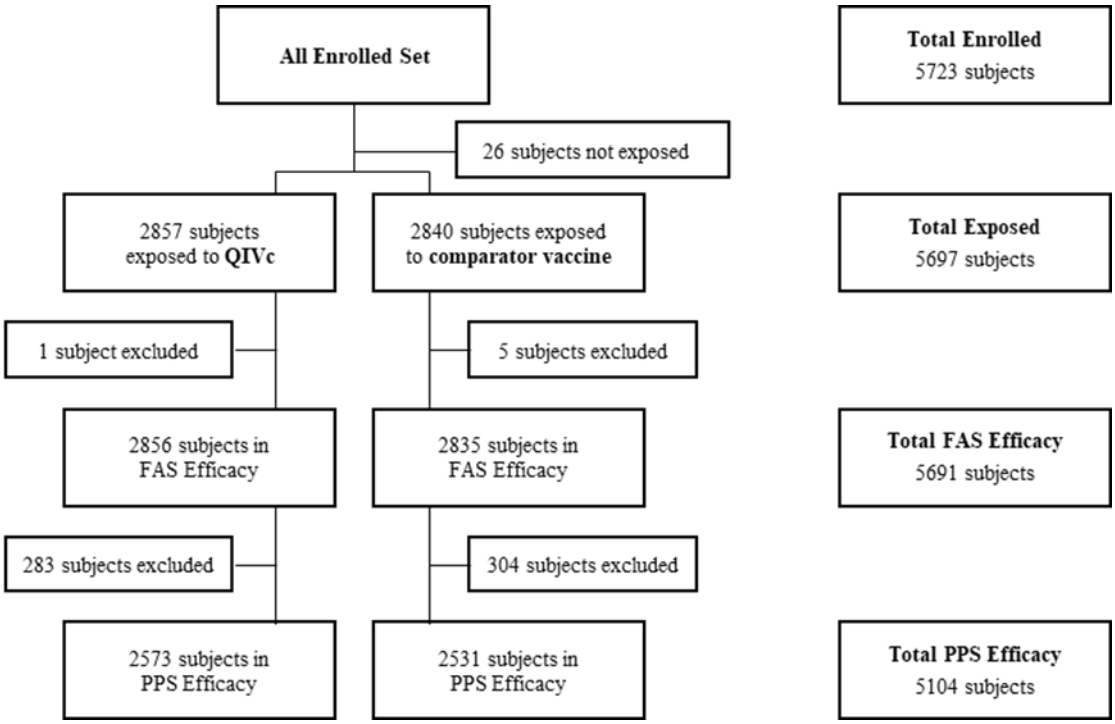
Results

Participant flow

A total of 5723 subjects 6 months through 47 months of age were enrolled in the study (All Enrolled Set) and randomized in a 1:1 ratio to receive QIVc or the comparator vaccine. Of the 5723 randomized subjects, 26 subjects did not receive study vaccine. In total, 5697 subjects received at least one study vaccination (All Exposed Set).

The majority of subjects (97.2%) completed the study; 163 (2.8%) subjects discontinued from the study. The most common reasons for discontinuing from the study was withdrawal of consent (1.4%) followed by lost to follow up (0.8%).

Figure 1



Source: Section 5.3.5.1, V130_14 CSR, Figure 10-1.
Abbreviations: FAS = Full Analysis Set; PPS = Per Protocol Set; QIVc = cell-based quadrivalent subunit influenza virus vaccine.

Recruitment

Subjects were randomized in a 1:1 ratio to receive QIVc or the non-influenza vaccine comparator (meningococcal group C polysaccharide conjugate vaccine [MenC vaccine]; NeisVac-C). Randomization was stratified by age, with a planned distribution of at least 30% of subjects aged 6 months through 23 months and at least 30% of subjects aged 24 months through 47 months. Enrolled subjects were also stratified by influenza vaccination history ("previously vaccinated" and "not previously vaccinated") to allow for assignment of the appropriate number of doses of study vaccine.

Conduct of the study

Study V130_14 was conducted over 5 influenza seasons at 75 centers in 15 countries. The study was performed during the Southern Hemisphere (SH) 2019, Northern Hemisphere (NH) 2019/2020, NH 2020/2021, NH 2022/2023, and SH 2023 influenza seasons.

Table 3 Study disposition-As Randomised-All enrolled set, study V130_14

	QIVc N=2860 n (%)	Comparator N=2863 n (%)	Total N=5723 n (%)
Total number of subjects enrolled	2860 (100)	2863 (100)	5723 (100)
Total number of subjects exposed	2857 (99.9)	2840 (99.2)	5697 (99.5)
Completed protocol	2794 (97.7)	2766 (96.6)	5560 (97.2)
Primary reason for discontinuation from the study	66 (2.3)	97 (3.4)	163 (2.8)
Adverse event	0	0	0
Death	1 (<0.1)	2 (0.1)	3 (0.1)
Withdrawal of consent	37 (1.3)	45 (1.6)	82 (1.4)
Lost to follow-up	19 (0.7)	25 (0.9)	44 (0.8)
Protocol deviation	0	2 (0.1)	2 (<0.1)
Study Terminated by Sponsor	0	0	0
Other	9 (0.3)	23 (0.8)	32 (0.6)

Source: Section 5.3.5.1, V130_14 CSR, Table 10-1.

Abbreviations: QIVc = cell-based quadrivalent subunit influenza virus vaccine.

Note 1: As randomized: according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received. One subject was randomized to the QIVc group, but received the comparator vaccine at Visit 1; this subject is included in the QIVc group "as randomized" and in the comparator vaccine group "as treated".

Baseline data

Demographic and baseline characteristics of the FAS Efficacy are summarized in Table 4. The demographic and baseline characteristics of the FAS Efficacy were consistent with those of the All Enrolled Set.

The mean (standard deviation) age of the study population in the FAS Efficacy was 25.9 (11.9) months and the range was 6 months to 47 months of age, which was consistent with the intended study population. The planned age distribution of at least 30% of subjects in each age subgroup was achieved: 44.2% of subjects were 23 months of age or younger and 55.8% of subjects were 24 months of age or older.

Overall, only 1.9% of subjects were previously vaccinated against influenza (and thus scheduled to receive 1 dose of study vaccine) and 98.1% of subjects were not previously vaccinated against influenza (and thus scheduled to receive 2 doses of study vaccine).

There were no notable differences in the distribution of demographic and baseline characteristics between the QIVc group and the comparator vaccine group in the FAS Efficacy.

The demographic and baseline characteristics of the FAS Immunogenicity were also generally balanced between the QIVc group and the comparator vaccine group, and were consistent with those of the All Enrolled Set, apart from the percentage of White subjects being higher in the FAS Immunogenicity compared with the All Enrolled Set (58.3% vs 43.2%); this likely reflects >50% of subjects in the FAS Immunogenicity being enrolled in Estonia (Section 5.3.5.1, V130_14 CSR, Section 10.4.1).

Table 4 Demographics and Baseline Characteristics in Subjects 6 Months Through 47 Months of Age – As Randomized – FAS Efficacy, Study V130_14

	QIVc N=2856	**Comparator N=2835**	**Total N=5691**
Age (months)			
n	2856	2835	5691
Mean (SD)	25.8 (11.9)	26.0 (11.9)	25.9 (11.9)
Min, max	6, 47	6, 47	6, 47
Age group (n [%])			
n	2856	2835	5691
6 months through 23 months	1266 (44.3)	1249 (44.1)	2515 (44.2)
24 months through 47 months	1590 (55.7)	1586 (55.9)	3176 (55.8)
Sex (n [%])			
n	2856	2835	5691
Male	1439 (50.4)	1514 (53.4)	2953 (51.9)
Female	1417 (49.6)	1321 (46.6)	2738 (48.1)
Race (n [%])			
n	2856	2835	5691
American Indian or Alaska Native	0	0	0
Asian	1098 (38.4)	1086 (38.3)	2184 (38.4)
Black or African American	348 (12.2)	343 (12.1)	691 (12.1)
Native Hawaiian or Other Pacific Islander	0	1 (<0.1)	1 (<0.1)
White	1235 (43.2)	1225 (43.2)	2460 (43.2)
Other	175 (6.1)	180 (6.3)	355 (6.2)
Ethnic Origin (n [%])			
n	2856	2835	5691
Hispanic or Latino	155 (5.4)	155 (5.5)	310 (5.4)
Not Hispanic or Latino	2692 (94.3)	2671 (94.2)	5363 (94.2)
Not reported	2 (0.1)	4 (0.1)	6 (0.1)
Unknown	7 (0.2)	5 (0.2)	12 (0.2)
Previous influenza vaccination (n [%])			
n	2856	2835	5691
Previously vaccinated	48 (1.7)	62 (2.2)	110 (1.9)
Not previously vaccinated	2808 (98.3)	2773 (97.8)	5581 (98.1)
Body mass index (kg/m^2)			
n	2855	2834	5689
Mean (SD)	16.50 (2.2)	16.61 (2.9)	16.56 (2.6)
Median	16.3	16.4	16.3

	QIVc N=2856	Comparator N=2835	Total N=5691
Season			
n	2856	2835	5691
Season 1	344 (12.0)	347 (12.2)	691 (12.1)
Season 2	495 (17.3)	484 (17.1)	979 (17.2)
Season 3	523 (18.3)	518 (18.3)	1041 (18.3)
Season 4	496 (17.4)	501 (17.7)	997 (17.5)
Season 5	998 (34.9)	985 (34.7)	1983 (34.8)
Country			
n	2856	2835	5691
Bangladesh	101 (3.5)	99 (3.5)	200 (3.5)
Bulgaria	130 (4.6)	135 (4.8)	265 (4.7)
Czech Republic	41 (1.4)	38 (1.3)	79 (1.4)
Estonia	625 (21.9)	620 (21.9)	1245 (21.9)
Honduras	147 (5.1)	149 (5.3)	296 (5.2)
Latvia	3 (0.1)	2 (0.1)	5 (0.1)
Malaysia	31 (1.1)	34 (1.2)	65 (1.1)
New Zealand	7 (0.2)	7 (0.2)	14 (0.2)
Pakistan	279 (9.8)	280 (9.9)	559 (9.8)
Philippines	608 (21.3)	601 (21.2)	1209 (21.2)
Poland	215 (7.5)	215 (7.6)	430 (7.6)
Romania	38 (1.3)	33 (1.2)	71 (1.2)
South Africa	376 (13.2)	373 (13.2)	749 (13.2)
Thailand	72 (2.5)	69 (2.4)	141 (2.5)
Ukraine	183 (6.4)	180 (6.3)	363 (6.4)

Source: Section 5.3.5.1, V130_14 CSR, Table 10-7.

Abbreviations: QIVc = cell-based quadrivalent subunit influenza virus vaccine; NH = Northern Hemisphere; SD = standard deviation; SH = Southern Hemisphere.

Note 1: As randomized: according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received.

Numbers analysed

All Enrolled Set

The All Enrolled Set was defined as all screened subjects who provided informed consent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a Subject ID.

FAS Efficacy

The primary and secondary efficacy objectives were assessed in the FAS Efficacy, which consisted of all subjects in the All Enrolled Set who were randomized, received at least one dose of study vaccination, and were evaluated for efficacy at more than 14 days after the last vaccination.

FAS Immunogenicity

Immunogenicity was assessed in a subset of subjects participating in the study, with approximately 222 subjects allocated to the immunogenicity subset per influenza season. The secondary immunogenicity objective was assessed in the FAS Immunogenicity, which consisted of all subjects in the All Enrolled Set

who were randomized, received at least one study vaccination, and provided evaluable serum samples at both baseline (Day 1) and 28 days after last vaccination (Day 29/57).

PPS Efficacy / PPS Immunogenicity

The efficacy and immunogenicity objectives were also assessed in the Per Protocol Set (PPS). The PPS Efficacy/Immunogenicity consisted of all subjects in the FAS Efficacy/Immunogenicity who correctly received the study vaccine (ie, received the study vaccine to which the subject was randomized and at the scheduled time points) and had no protocol deviations leading to exclusion or were not excluded due to other reasons as defined prior to unblinding/analysis.

The analysis populations are presented in Table 5 below.

Table 5 Overview of Efficacy and Immunogenicity sets analysed-as randomised, Study V130_14

	QIVc N=2860 n (%)	**Comparator N=2863 n (%)**	**Total N=5723 n (%)**
All Enrolled Set	2860 (100)	2863 (100)	5723 (100)
All Exposed Set	2857 (99.9)	2840 (99.2)	5697 (99.5)
FAS Efficacy	2856 (99.9)	2835 (99.0)	5691 (99.4)
PPS Efficacy	2573 (90.0)	2531 (88.4)	5104 (89.2)
Immunogenicity Subset	536	529	1065
FAS Immunogenicity	525 (97.9)	524 (99.1)	1049 (98.5)
PPS Immunogenicity	496 (92.5)	498 (94.1)	994 (93.3)

Source: Section 5.3.5.1, V130_14 CSR, Table 10-3.

Abbreviations: FAS = Full Analysis Set; PPS = Per Protocol Set; QIVc = cell-based quadrivalent subunit influenza virus vaccine.

Note 1: As randomized: according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received.

A total of 5723 study participants were enrolled in the study. There were only 2.8% of subjects who discontinued the study, and this is adequate. Nevertheless, it is noted that the number of subjects that did not receive any study vaccine at all is significantly higher for the Comparator than for the QIVc group: 21 (0.7%) vs 2 (0.1%). According to the MAH, the main reason for the imbalance between groups was due to an insufficient supply of the comparator vaccine.

The baseline characteristics of the enrolled subjects were well balanced between treatment groups. The planned age distribution of at least 30% of subjects in each age subgroup was achieved: 44.2% of subjects were 23 months of age or younger and 55.8% of subjects were 24 months of age or older. Only 1.9% of the subjects had been previously vaccinated against influenza and received 1 dose of study vaccine. Therefore, 98.1% received 2 vaccine doses. This very high proportion of non-previously vaccinated participants reflects the very low influenza vaccination that takes place in this age group. All other baseline and demographic characteristics are well balanced between the QIVc and the comparator group. There are some races and ethnic origins that are more represented than others but is this not expected to impact in the study results. For instance, it is noted that more than half of the participants in the FAS Immunogenicity set are Estonian. Nevertheless, it is not expected to have an impact on the immunogenicity results.

Efficacy objectives were assessed in the FAS efficacy population. The use of the PPS (Per Protocol Set) for the efficacy assessment would have been optimal, and it is observed that there is around a 10% difference between the FAS and the PPS populations (for the FAS efficacy, n=2856 (99.9%) in QIVc and n=2835 (99.0%) in the comparator whereas in the PPS n=2573 (90.0%) in QIVc and n=2531 (88.4%)

in the comparator. Moreover, the PPS excludes all participants that have been excluded because of protocol deviations or other reasons. The MAH submitted the results of the efficacy analyses of the primary endpoints in both the FAS and PPS populations to justify the use of the FAS populations instead of the PPS for the efficacy analysis and they were similar. In addition, the choice of the FAS population is consistent with the ICH E9. Therefore, the use of the FAS population to assess efficacy is endorsed.

Outcomes and estimation

EFFICACY

In the FAS Efficacy, 1096 of 2856 (38.4%) subjects in the QIVc group and 1175 of 2835 (41.4%) subjects in the comparator vaccine group reported one or more ILIs during the entire study period. There were 1813 ILIs reported in the QIVc group and 1943 ILIs reported in the comparator vaccine group, with the majority of ILIs reported during the primary endpoint surveillance period of >14 days after last vaccination to end of influenza season (QIVc: 1347/1813 ILIs, 74.3%; comparator vaccine: 1437/1943 ILIs, 74.0%).

For subjects with occurrence of an ILI during the primary endpoint surveillance period, 1339 swabs were collected for influenza testing in the QIVc group and 1427 swabs were collected in the comparator vaccine group. The most frequently reported ILI symptoms (in addition to having a temperature ≥37.8°C on the same day) for ILIs reported >14 days after last vaccination to end of influenza season were rhinorrhoea (QIVc: 1088/1347 ILIs, 80.8%; comparator vaccine: 1172/1437 ILIs, 81.6%) and cough (QIVc: 970/1347 ILIs, 72.0%; comparator vaccine: 1044/1437 ILIs, 72.7%) in both vaccine groups. The vast majority of swabs were collected via the NP route (QIVc: 98.6%; comparator vaccine: 98.7%).

Primary Efficacy Analysis

The following primary efficacy endpoints were evaluated for QIVc compared to a non-influenza vaccine in subjects 6 months through 47 months of age:

1a First occurrence of RT-PCR confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.

1b First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.

The primary efficacy objective would be achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints, that is, if the LL of the two-sided 97.5% CI of VE was greater than 0%.

To account for the interim analysis conducted after Season 3 of the study and maintain the overall alpha of 1.25% (one-sided), the CIs for the aVE estimate associated with the primary efficacy objectives were adjusted. Based on this, the CI for primary efficacy endpoint 1a was adjusted from 97.5% to 97.98%, while the CI for primary efficacy endpoint 1b remained at 97.5%.

In the FAS Efficacy, the number of cases of RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, was 104 in the QIVc group and 173 in the comparator vaccine group (Table 5). For this endpoint, the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 41.26% (97.98% CI: 21.55, 56.02) (Table 5). The pre-specified success criterion to demonstrate efficacy for this primary endpoint was met as the LL of the two-sided 97.98% CI was above 0%.

The number of cases of culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to vaccine strain was 44 in the QIVc group and 82 in the comparator vaccine group (Table 5). For this endpoint, the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 46.90% (97.5% CI: 19.19, 65.11) (Table 5). The pre-specified success criterion to demonstrate efficacy for this primary endpoint was met as the LL of the two-sided 97.5% CI was above 0%.

The primary objective of efficacy was considered to be achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints. Both primary efficacy endpoints met the success criteria. The primary objective of the study was achieved.

Table 6 Number of Subjects with First-Occurrence RT-PCR Confirmed Influenza, Number of Subjects with First-Occurrence Culture Confirmed Influenza (Antigenically Matched), and Absolute Vaccine Efficacy in Subjects 6 Months Through 47 Months of Age – As Randomized – FAS Efficacy, Study V130_14

	QIVc N=2856	Comparator N=2835	aVE[a] (%) (97.98% CI)	Success Criteria Met (Yes/No)
RT-PCR Confirmed Influenza Any Type A and/or Type B strain[b] Number of cases (attack rate)	104 (3.64)	173 (6.10)	41.26 (21.55, 56.02)	Yes
	QIVc N=2856	**Comparator N=2835**	**aVE[a] (%) (97.5% CI)**	**Success Criteria Met (Yes/No)**
Culture Confirmed Influenza Antigenically matched to vaccine strain[c] Number of cases (attack rate)	44 (1.54)	82 (2.89)	46.90 (19.19, 65.11)	Yes

Source: Section 5.3.5.1, V130_14 CSR, Table 11-2.

Abbreviations: aVE = absolute vaccine efficacy; CI = confidence interval; FAS = Full Analysis Set; ILI = influenza-like illness; QIVc = cell-based quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription-polymerase chain reaction.

[a] Adjusted aVE, estimated from a Cox proportional hazard model for time from >14 days after the last study vaccination to the onset of the first occurrence of RT-PCR confirmed influenza (or culture confirmed influenza antigenically matched to the vaccine strain) with vaccine group as the main effect, adjusting for previous vaccination status, sex, country, and season as random effects.

[b] RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine occurring at >14 days after the last vaccination in the treatment period until the end of the influenza season, in association with protocol-defined ILI symptoms.

c Culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to the influenza strains selected for the seasonal influenza vaccine occurring at >14 days after the last vaccination in the treatment period until the end of the influenza season, in association with protocol-defined ILI symptoms.

Note 1: As randomized: according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received.

The results of the primary efficacy analyses in the PPS Efficacy were consistent with the results in the FAS Efficacy, supporting the robustness of the efficacy findings. In the PPS Efficacy, the aVE for first-occurrence RT PCR confirmed influenza regardless of antigenic match to vaccine strain was 43.96% (97.98% CI: 24.17, 58.59, based on 256 observed cases) and the aVE for first-occurrence culture confirmed influenza due to antigenically matched vaccine strain was 47.56% (97.5% CI: 18.56, 66.23, based on 115 observed cases).

Secondary Efficacy Analysis

The following secondary efficacy endpoints were evaluated for QIVc compared to a non-influenza vaccine in subjects 6 months through 47 months of age:

- First occurrence of culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.

- First occurrence of culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.

- First occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season.

The secondary efficacy objectives were assessed in the FAS Efficacy and were not associated with any hypothesis testing.

For first occurrence of culture confirmed influenza due to influenza virus strains that were antigenically dissimilar to the vaccine strains (ie, unmatched strains), the aVE observed for QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 54.49% (95% CI: 22.55, 73.26, based on 63 observed cases) (Table 7).

For first occurrence of culture confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strains, the aVE observed for QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 50.67% (95% CI: 32.83, 63.77, based on 182 observed cases) (Table 7).

Table 7 Number of Subjects with First-Occurrence Culture Confirmed Influenza (Unmatched Strain and Any Strain), and Absolute Vaccine Efficacy in Subjects 6 Months Through 47 Months of Age – As Randomized – FAS Efficacy, Study V130_14

Culture Confirmed Influenza	QIVc N=2856	Comparator N=2835	aVE[a] (%) (95% CI)
Unmatched Strain[b]	20 (0.70)	43 (1.52)	54.49 (22.55, 73.26)
Number of cases (attack rate)			
Any Strain[c]	61 (2.14)	121 (4.27)	50.67 (32.83, 63.77)
Number of cases (attack rate)			

Source: Section 5.3.5.1, V130_14 CSR, Table 11-3.

Abbreviations: aVE = absolute vaccine efficacy; CI = confidence interval; FAS = Full Analysis Set; QIVc = cell-based quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription-polymerase chain reaction.

[a] Adjusted aVE, estimated from a Cox proportional hazard model with vaccine group as the main effect, adjusting for age group, previous vaccination status, country, and season as random effects. Note that the age group is from planned stratification.

[b] Culture confirmed influenza due to influenza Type A and/or Type B virus antigenically unmatched to the influenza strains selected for the seasonal influenza vaccine occurring at >14 days after the last vaccination until the end of the influenza season, in association with protocol-defined ILI symptoms.

[c] Culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine occurring at >14 days after the last vaccination until the end of the influenza season, in association with protocol-defined ILI symptoms. There were 3 subjects in the QIVc group and 3 subjects in the comparator vaccine group with first-occurrence culture confirmed influenza that was a coinfection with matched and unmatched influenza strains; each of these subjects was counted only once in the overall Any Strain category. There was 1 additional subject in the comparator vaccine group with first-occurrence culture confirmed influenza (unmatched strain), followed by a first-occurrence culture confirmed influenza event (matched strain). Only the first event was counted in the overall Any Strain category.

Note 1: As randomized: according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received.

For first occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, there were 0 cases in the QIVc group and 9 cases in the comparator vaccine group. Of the 9 cases in the comparator vaccine group, 5 cases were physician-confirmed acute otitis media and 4 cases were physician-confirmed lower respiratory tract illness. The aVE point estimate for RT-PCR confirmed moderate-to-severe influenza in subjects 6 months through 47 months of age was 100%; however, the counts were too small to draw any firm conclusion (Table 8).

Table 8 Number of Subjects with First Occurrence of Moderate-to-Severe RT-PCR Confirmed Influenza and Absolute Vaccine Efficacy in Subjects 6 Months Through 47 Months of Age – As Randomized – FAS Efficacy, Study V130_14

	QIVc N=2856	Comparator N=2835	aVE[a] (95% CI)
Any Strain – Number of cases (attack rate)	0	9 (0.32)	100 (NE, 100)

Source: Section 5.3.5.1, V130_14 CSR, Table 11-4.

Abbreviations: aVE = absolute vaccine efficacy; CI = confidence interval; FAS = Full Analysis Set; ICU = intensive care unit; ILI = influenza-like illness; NE = not estimable; QIVc = cell-based quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription-polymerase chain reaction.

[a] Adjusted aVE, estimated from a Cox proportional hazard model for time from >14 days after the last study vaccination to the onset of the first occurrence of Moderate-Severe RT-PCR confirmed influenza with vaccine group as the main effect, adjusting for, previous vaccination status, sex, country and season as random effects.

Note 1: As randomized: according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received.

Note 2: A moderate-to-severe ILI episode is defined as an ILI episode complicated by one of the following diagnoses within 30 days after the ILI onset: physician confirmed lower respiratory tract illness, physician confirmed acute otitis media, or

hospitalization in the ICU, physician-diagnosed serious extra-pulmonary complication of influenza or supplemental oxygen requirement for more than 8 hours.

Additional Analysis by Strain

Efficacy of first occurrence RT-PCR confirmed influenza (due to any influenza Type A or Type B virus, regardless of antigenic match to vaccine strain) was analysed by virus strain (ie, A/H1N1, A/H3N2, B/Yamagata, and B/Victoria) (*Table 9*). There were some clinical isolates that only provided an RT-PCR confirmed Type A or Type B result and were unable to provide a subtype result in the RT-PCR subtype assays. Overall, there were more RT-PCR confirmed Type A than Type B influenza cases, and the point estimates of aVE for the Type A subtypes, A/H1N1 and A/H3N2, were observed to be higher than for B/Victoria. Only 4 cases of B/Yamagata were detected during the 5-season study, all from the SH 2019 season, which is consistent with there being no confirmation of B/Yamagata in circulation since March 2020 (Paget et al. 2022).

Not all RT-PCR influenza confirmed cases were able to be sufficiently propagated in Madin-Darby Canine Kidney (MDCK) cultures to allow for antigenic characterization. The observed efficacy for first occurrence culture confirmed cases for any strain (ie, either matched or unmatched to vaccine strain) by virus strain was similar for the Type A subtypes and B/Victoria, with aVE of 47.16% (95% CI: 14.08, 67.50) for the A/H1N1 strain, 46.13% (95% CI: 11.30, 67.28) for the A/H3N2 strain, and 56.04% (95% CI: 15.34, 77.17) for the B/Victoria strain. Efficacy for the B/Yamagata strain could not be estimated. For first occurrence culture confirmed cases for matched strain, the highest point estimate of aVE was observed for B/Victoria, whereas for first occurrence culture confirmed cases for unmatched strain, the highest point estimate was observed for A/H3N2; however, the 95% CIs were wide given the smaller number of cases observed for the analyses by individual strain.

Table 9 Number of Subjects with First-Occurrence RT-PCR Confirmed Influenza, Number of Subjects with First-Occurrence Culture Confirmed Influenza (Matched Strain, Unmatched Strain, and Any Strain), and Absolute Vaccine Efficacy, Overall and by Strain, in Subjects 6 Months Through 47 Months of Age – As Randomized – FAS Efficacy, Study V130_14

	QIVc N=2856	Comparator N=2835	aVE[a] (CI[b])
RT-PCR Confirmed Influenza			
Any Strain[c] – Number of cases (attack rate)	**104 (3.64)**	**173 (6.10)**	**41.26 (21.55, 56.02)**
Type A[d]	79 (2.77)	141 (4.97)	45.17 (23.92, 60.48)
A/H1N1	25 (0.88)	56 (1.98)	55.91 (22.85, 74.81)
A/H3N2	34 (1.19)	67 (2.36)	50.53 (19.19, 69.72)
Type B[d]	31 (1.09)	42 (1.48)	26.36 (-27.84, 57.59)
B/Yamagata	1 (0.04)	3 (0.11)	64.66 (-419.33, 97.59)
B/Victoria	24 (0.84)	34 (1.20)	30.16 (-29.92, 62.45)
Culture Confirmed Influenza			
Matched Strain[e] – Number of cases (attack rate)	**44 (1.54)**	**82 (2.89)**	**46.90 (19.19, 65.11)**
A/H1N1	21 (0.74)	40 (1.41)	47.69 (4.19, 71.44)
A/H3N2	20 (0.70)	29 (1.02)	31.13 (-32.35, 64.16)
B/Yamagata	0	1 (0.04)	100 (NE, 100)
B/Victoria	3 (0.11)	13 (0.46)	77.26 (4.39, 94.59)
Unmatched Strain – Number of cases (attack rate)	**20 (0.70)**	**43 (1.52)**	**54.49 (22.55, 73.26)**

A/H1N1	4 (0.14)	7 (0.25)	43.44 (-93.27, 83.45)
A/H3N2	4 (0.14)	15 (0.53)	73.90 (21.30, 91.35)
B/Yamagata	1 (0.04)	0	NE (NE, 100)
B/Victoria	10 (0.35)	17 (0.60)	41.29 (-28.34, 73.15)
Any Strain – Number of cases (attack rate)	**61 (2.14)**	**121 (4.27)**	**50.67 (32.83, 63.77)**
A/H1N1	25 (0.88)	47 (1.66)	47.16 (14.08, 67.50)
A/H3N2	24 (0.84)	44 (1.55)	46.13 (11.30, 67.28)
B/Yamagata	1 (0.04)	1 (0.04)	-5.48 (-1601.53, 93.46)
B/Victoria	13 (0.46)	29 (1.02)	56.04 (15.34, 77.17)

Source: Section 5.3.5.1, V130_14 CSR, Table 11-5.

Abbreviations: aVE = absolute vaccine efficacy; CI = confidence interval; FAS = Full Analysis Set; QIVc = cell-based quadrivalent subunit influenza virus vaccine; NE = not estimable; RT-PCR = reverse transcription-polymerase chain reaction.

[a] Adjusted aVE, estimated from a Cox proportional hazard model for time from >14 days after the last study vaccination to the onset of the first occurrence of RT-PCR-confirmed influenza (or culture confirmed influenza antigenically matched to the vaccine strain) with vaccine group as the main effect, adjusting for age group, previous vaccination status, country, and season as random effects. Note that the age group is from planned stratification.

[b] 97.98% CI provided for aVE for the primary endpoint of RT-PCR confirmed influenza (any strain, Type A, Type B, and individual strains); 97.5% CI provided for aVE the primary endpoint of culture confirmed influenza (matched strain and individual strains); 95% CI provided for aVE for the secondary efficacy endpoints of culture confirmed influenza (unmatched strain and individual strains; any strain and individual strains).

[c] RT-PCR confirmed influenza, due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination in the treatment period until the end of the influenza season, in association with protocol-defined ILI symptoms.

[d] Some Type A and Type B strains could not be identified by PCR subtyping or lineage assessment, respectively, and are included in the Type A and Type B categories, respectively.

[e] Culture confirmed influenza, due to influenza Type A and/or Type B virus antigenically matched to the influenza strains selected for the seasonal influenza vaccine, occurring at >14 days after the last vaccination in the treatment period until the end of the influenza season, in association with protocol-defined ILI symptoms.

Note 1: As randomized: according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received.

Note 2: First-occurrence culture confirmed influenza/Matched Strain: In the comparator vaccine group, 1 subject had a first-occurrence culture confirmed influenza classified as coinfection with A/H1N1 (matched strain) and B/Yamagata (matched strain); this subject was included in both of the A/H1N1 and B/Yamagata subcategories, and counted only once in the overall Matched Strain category.

Note 3: First-occurrence culture confirmed influenza/Unmatched Strain: In the QIVc group, 1 subject had first-occurrence RT-PCR confirmed influenza classified as A/H3N2, which was not cultured confirmed, and was coinfected with RT-PCR confirmed influenza classified as Type B virus, which was culture confirmed as influenza unmatched to both B/Yamagata and B/Victoria; this subject was counted in the overall Unmatched Strain category only and not in any of the individual strain subcategories. In the comparator vaccine group, there were 2 subjects with first-occurrence RT-PCR confirmed influenza classified as Type A virus, subtype undetermined, which was culture confirmed as influenza unmatched to both A/H1N1 and A/H3N2, and there were 2 subjects with coinfection with first-occurrence culture confirmed influenza classified as A/H3N2 (matched strain) and RT-PCR confirmed influenza classified as Type B virus, lineage undetermined, which was culture confirmed as influenza unmatched to B/Victoria and B/Yamagata. These 4 subjects were counted in the overall Unmatched Strain category only and not in any of the individual strain subcategories.

Note 4: First occurrence culture confirmed influenza/Any Strain: There were 3 subjects in the QIVc group and 3 subjects in the comparator vaccine group with first-occurrence culture confirmed influenza that was a coinfection with matched and unmatched influenza strains; each of these subjects was counted only once in the overall Any Strain category. There was 1 additional subject in the comparator vaccine group with first-occurrence culture confirmed influenza (unmatched strain), followed by a first-occurrence culture confirmed influenza event (matched strain). Only the first event was counted in the overall Any Strain category.

Supplementary Efficacy Analysis

Prior to the completion of the influenza surveillance period for the fifth season of the study, the minimum number of RT-PCR confirmed primary endpoint influenza cases and the minimum number of antigenically matched culture confirmed primary endpoint influenza cases required for final efficacy analyses were

accrued, which allowed proceeding to the analyses of the primary efficacy endpoints. The additional NP swabs collected through the end of the SH 2023 influenza season (the fifth study season) underwent laboratory testing for influenza. Supplemental analyses were performed that included cumulative number of primary endpoint cases for Seasons 1 to 5 through the designated end of the influenza season and are provided for information only.

In the FAS Efficacy, the number of cases of RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, was 107 in the QIVc group and 177 in the comparator vaccine group. For this endpoint, the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 40.84% (97.5% CI: 22.07, 55.09).

The number of cases of culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to vaccine strain was 45 in the QIVc group and 85 in the comparator vaccine group. For this endpoint, the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 47.58% (97.5% CI: 20.67, 65.36).

These supplemental analyses support the robustness of the primary efficacy results.

The study protocol included the possibility to conduct an interim analysis when a certain number of PCR-confirmed ILIs were achieved. This took place after Season 3 of the study. In order to maintain the overall alpha of 1.25% (one-sided), the CIs for the aVE estimate associated with the primary efficacy objectives were to be adjusted. The CI for primary efficacy endpoint 1a was adjusted from 97.5% to 97.98%, and the CI for primary efficacy endpoint 1b remained at 97.5%. The MAH presented the information fractions used in the cumulative O'Brien-Fleming type error-spending-function and the calculations for the adjustments of the CI for primary endpoints 1a and 1b in the final analysis. The reason for adjusting only 1a and not both is justified.

Both pre-specified success criteria for the primary endpoints 1a and 1b were met, so absolute vaccine efficacy (aVE) was demonstrated for QIVc versus the non-influenza comparator vaccine. The primary objective of efficacy was considered to be achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints. Both primary efficacy endpoints met the success criteria, therefore the primary objective of the study was achieved. For RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 41.26% (97.98% CI: 21.55, 56.02). For culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to vaccine strain the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 46.90% (97.5% CI: 19.19, 65.11).

The primary efficacy results in the PPS Efficacy population were consistent with the previously shown results (from the FAS Efficacy).

The secondary objectives, culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza strains in the vaccine, culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match and RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match, were also met.

For first occurrence of culture confirmed influenza due to influenza virus strains that were antigenically dissimilar to the vaccine strains (ie, unmatched strains), the aVE observed was 54.49% (95% CI: 22.55, 73.26). For first occurrence of culture confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strains, the aVE was 50.67% (95% CI: 32.83, 63.77). For first occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, there were 0 cases in the QIVc group and 9 cases in the comparator vaccine group. The aVE point was 100%; however because of the low numbers, results must be taken with caution.

Interestingly, the point estimate for aVE for culture confirmed influenza due to strains dissimilar to those in the vaccine (54.49% [95% CI: 22.55, 73.26]) was higher than the aVE results obtained in the analysis of the primary endpoints.

Additionally, efficacy analysis by strain was carried out, although not all clinical isolates could provide cell culture results. Results by strain were consistent with the overall efficacy results for both type A viruses (H1N1 and H3N2) and for type B Victoria lineage. Efficacy against B/Yamagata could not be determined due to the very low cases (only 4 cases of B/Yamagata in the 5 seasons), which is consistent with the failure to detect B/Yamagata viruses since March 2020. In any case, confidence intervals were wide due to the smaller number of cases.

The minimum number of RT-PCR confirmed cases and of antigenically matched culture confirmed cases required for final efficacy analysis were obtained before the end of the fifth influenza season. Therefore, the analysis was carried out without the analysis of the totality of the samples that were finally collected. These extra cases and their analysis were provided for information only. This approach is endorsed.

IMMUNOGENICITY RESULTS

The secondary immunogenicity objective was to evaluate the immune response to QIVc each study season. Sera were collected before and 4 weeks after last vaccination in a subset of subjects 6 months through 47 months of age in each study vaccine group. In total, 1049 subjects were included in the FAS Immunogenicity (220 in Season 1, 218 in Season 2, 223 in Season 3, 172 in Season 4, and 216 in Season 5). The immune response to each of the 4 QIVc vaccine strains selected for the season was assessed via the following endpoints: pre- and postvaccination geometric mean titers (GMTs); geometric mean ratio (GMR); and seroconversion rate (SCR).

Immunogenicity was assessed at baseline (Day 1, before vaccination) and at Day 29 (previously vaccinated subjects receiving a single dose of study vaccine) or Day 57 (not previously vaccinated subjects receiving 2 doses of study vaccine) for all 4 influenza vaccine strains, using the HI and MN assays validated for the season.

The vaccine strains for QIVc could change from season to season, based on the World Health Organization (WHO) strain recommendations for the particular influenza season. The A/H1N1 strain in the vaccine changed each season; the A/H3N2 strain changed each season, apart from being the same strain for Season 4 (NH 2022/2023) and Season 5 (SH 2023); the B/Yamagata strain was the same strain for the 5 study seasons; and the B/Victoria strain was the same for the first 2 seasons (SH 2019 and NH 2019/2020), changed for Season 3 (NH 2020/2021), and changed for Season 4 (NH 2022/2023), remaining the same strain for Season 5 (SH 2023). The immunogenicity results are therefore presented by season, even if a specific vaccine strain did not change between seasons. The immunogenicity endpoints were analysed descriptively for each season.

The A/H3N2 strain did not agglutinate red blood cells in the HI assay for Seasons 1 and 3 (Table 9); therefore, the primary immunogenicity assay for the A/H3N2 strain was the MN assay, which was performed for all 5 study seasons.

Hemagglutination Inhibition Assay

Geometric Mean Titers

Day 1:

- For each of the 5 influenza seasons, the Day 1 HI GMTs were not notably different between the QIVc and comparator vaccine groups for any of the A/H1N1, B/Yamagata, or B/Victoria strains
- The Day 1 HI GMTs for the A/H1N1 strain varied across the 5 seasons.
- The Day 1 HI GMTs for the B/Yamagata and B/Victoria strains were similar across the 5 seasons and were observed to be lower values than those for the A/H1N1 strain.
- For the 3 seasons with A/H3N2 HI data, the Day 1 HI GMTs were not notably different between the QIVc and comparator vaccine groups and the Day 1 HI GMTs varied across the 3 seasons.

Day 29/57:

- In the QIVc group, the Day 29/57 HI GMTs were observed to be higher than the Day 1 HI GMTs across the 5 seasons for each of the A/H1N1, B/Yamagata, and B/Victoria strains (Table 9).
- In the comparator vaccine group, the HI GMTs at Day 29/57 were not notably different from Day 1 HI GMTs across the seasons for the A/H1N1, B/Yamagata, and B/Victoria strains, with variability observed for A/H1N1 Day 29/57 GMTs across the seasons and for B/Victoria in Season 5 as compared to the other study seasons.
- The Day 29/57 HI GMTs were observed to be higher in the QIVc group compared with the comparator vaccine group across the 5 seasons for each of the A/H1N1, B/Yamagata, and B/Victoria strains. Day 29/57 HI GMTs in Season 5 were observed to be higher values than those from other seasons.
- For the 3 seasons with A/H3N2 HI data, the Day 29/57 HI GMTs were observed to be higher than the Day 1 HI GMTs in the QIVc group and Day 29/57 HI GMTs were observed to be higher in the QIVc group compared with the comparator vaccine group.

Geometric Mean Ratios

- For each of the 5 influenza seasons, the HI GMRs were observed to be higher in the QIVc group than in the comparator vaccine group for each of the A/H1N1, B/Yamagata, B/Victoria strains (Table 9).
- In the QIVc group, the GMRs varied across the 5 seasons, with the highest GMRs for each of the A/H1N1, B/Yamagata, and B/Victoria strains observed for Season 5.
- In the QIVc group, the GMRs for the B/Yamagata and B/Victoria strains were observed to be similar to or lower than those for the A/H1N1 strain.
- In the comparator vaccine group, the GMRs were observed to be similar across the seasons for A/H1N1, B/Yamagata, and B/Victoria strains, with variability observed in Season 5 for A/H1N1 and B/Victoria.

- For the 3 seasons with A/H3N2 HI data, the GMRs were higher for the QIVc group compared to the comparator group, with the GMR for Season 4 lower than the GMRs for Seasons 2 and 5.

Seroconversion Rates

- For each of the 5 influenza seasons, the HI SCRs were observed to be higher in the QIVc group than in the comparator vaccine group for each of the A/H1N1, B/Yamagata, and B/Victoria strains (Table 9).

- In the QIVc group, the SCR varied across the 5 seasons, with the highest SCR for each of the A/H1N1. B/Yamagata, and B/Victoria strains observed for Season 5.

- For the 3 seasons with A/H3N2 HI data, the SCRs were observed to be higher in the QIVc group than in the comparator vaccine group, with the highest SCR observed for Season 5.

Table 10 Pre- and Postvaccination GMT, GMR, and SCR in Subjects 6 Months Through 47 Months of Age (HI Assay Data) – As Randomized – FAS Immunogenicity, Study V130_14

Season	Season 1		Season 2		Season 3		Season 4		Season 5	
Any Strain	**QIVc No. or % (95% CI)**	**Comparator No. or % (95% CI)**	**QIVc No. or % (95% CI)**	**Comparator No. or % (95% CI)**	**QIVc No. or % (95% CI)**	**Comparator No. or % (95% CI)**	**QIVc No. or % (95% CI)**	**Comparator No. or % (95% CI)**	**QIVc No. or % (95% CI)**	**Comparator No. or % (95% CI)**
A/H1N1	**N=112**	**N=108**	**N=107**	**N=111**	**N=111**	**N=112**	**N=87**	**N=85**	**N=108**	**N=108**
Day 1 HI GMT	40.06 (21.41, 74.97)	44.28 (24.19, 81.07)	22.99 (9.52, 55.49)	27.50 (11.60, 65.18)	10.15 (4.45, 23.13)	8.72 (3.87, 19.60)	57.83 (34.41, 97.19)	58.00 (34.81, 96.64)	13.60 (1.97, 93.97)	13.94 (1.95, 99.61)
Day 29/57 HI GMT	126.39 (68.37, 233.66)	60.33 (33.32, 109.21)	60.77 (33.77, 109.38)	11.24 (6.32, 20.02)	49.38 (22.92, 106.39)	5.45 (2.56, 11.58)	149.01 (96.96, 229.01)	81.71 (53.55, 124.68)	362.71 (74.42, 1767.89)	60.84 (12.14, 304.84)
GMR HI Titer	3.36 (1.69, 6.66)	1.53 (0.79, 2.95)	3.71 (2.04, 6.73)	0.67 (0.37, 1.20)	6.28 (2.91, 13.56)	0.70 (0.33, 1.50)	2.59 (1.51, 4.45)	1.42 (0.83, 2.41)	19.20 (3.61, 102.12)	3.20 (0.58, 17.52)
SCR (%) HI Titer	45.54 (36.10, 55.22)	12.04 (6.57, 19.70)	57.01 (47.08, 66.54)	3.60 (0.99, 8.97)	68.47 (58.96, 76.96)	2.68 (0.56, 7.63)	29.89 (20.54, 40.65)	4.71 (1.30, 11.61)	75.00 (65.75, 82.83)	12.96 (7.27, 20.79)
A/H3N2	**NA**	**NA**	**N=107**	**N=111**	**NA**	**NA**	**N=87**	**N=85**	**N=108**	**N=108**
Day 1 HI GMT	**NA**	**NA**	12.21 (5.59, 26.70)	14.14 (6.57, 30.41)	**NA**	**NA**	46.38 (21.09, 101.98)	35.62 (16.41, 77.30)	82.67 (19.98, 342.16)	120.80 (28.47, 512.58)
Day 29/57 HI GMT	**NA**	**NA**	95.36 (43.91, 207.07)	8.79 (4.11, 18.77)	**NA**	**NA**	67.88 (36.64, 125.77)	38.85 (21.22, 71.10)	440.30 (127.04, 1526.08)	57.87 (16.29, 205.63)
GMR HI Titer	**NA**	**NA**	7.43 (2.95, 18.75)	0.62 (0.25, 1.54)	**NA**	**NA**	1.81 (0.86, 3.81)	1.19 (0.57, 2.48)	7.14 (1.81, 28.16)	0.80 (0.20, 3.24)
SCR (%) HI Titer	**NA**	**NA**	70.09 (60.48, 78.56)	6.31 (2.57, 12.56)	**NA**	**NA**	44.83 (34.15, 55.87)	28.24 (19.00, 39.04)	84.26 (76.00, 90.55)	15.74 (9.45, 24.00)
B/Yamagata	**N=112**	**N=108**	**N=107**	**N=111**	**N=111**	**N=111**	**N=87**	**N=85**	**N=108**	**N=108**
Day 1 HI GMT	11.66 (8.26, 16.46)	11.53 (8.27, 16.09)	9.87 (6.86, 14.22)	8.22 (5.75, 11.75)	7.65 (4.25, 13.79)	7.54 (4.19, 13.57)	8.96 (6.78, 11.84)	9.49 (7.22, 12.48)	7.30 (4.19, 12.73)	7.35 (4.18, 12.95)
Day 29/57 HI GMT	18.94 (13.07, 27.46)	6.90 (4.82, 9.87)	23.65 (14.04, 39.85)	13.57 (8.17, 22.53)	13.85 (6.91, 27.77)	5.26 (2.63, 10.53)	13.80 (8.95, 21.28)	4.70 (3.06, 7.22)	53.72 (20.85, 138.40)	8.04 (3.07, 21.06)
GMR HI Titer	2.52 (1.75, 3.63)	0.92 (0.65, 1.31)	3.38 (2.02, 5.67)	1.96 (1.18, 3.25)	1.95 (0.91, 4.15)	0.75 (0.35, 1.59)	2.03 (1.32, 3.13)	0.68 (0.44, 1.04)	8.04 (3.12, 20.72)	1.20 (0.46, 3.15)
SCR (%) HI Titer	37.50 (28.53, 47.15)	3.70 (1.02, 9.21)	24.30 (16.53, 33.54)	6.31 (2.57, 12.56)	23.42 (15.91, 32.41)	0.90 (0.02, 4.92)	29.89 (20.54, 40.65)	1.18 (0.03, 6.38)	66.67 (56.95, 75.45)	3.70 (1.02, 9.21)

Season	Season 1		Season 2		Season 3		Season 4		Season 5	
Any Strain	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)
B/Victoria	**N=112**	**N=108**	**N=107**	**N=111**	**N=111**	**N=112**	**N=87**	**N=85**	**N=108**	**N=108**
Day 1 HI GMT	7.40 (5.35, 10.24)	8.36 (6.11, 11.43)	9.37 (7.46, 11.76)	9.31 (7.45, 11.63)	8.34 (5.40, 12.90)	9.39 (6.12, 14.42)	5.82 (5.18, 6.53)	6.08 (5.42, 6.82)	7.84 (1.38, 44.61)	5.92 (1.01, 34.73)
Day 29/57 HI GMT	14.97 (10.42, 21.49)	7.01 (4.94, 9.95)	16.84 (11.32, 25.07)	8.82 (5.97, 13.02)	9.54 (5.60, 16.25)	4.88 (2.89, 8.26)	23.92 (13.98, 40.92)	4.67 (2.73, 7.97)	539.53 (158.62, 1835.19)	45.34 (13.01, 157.93)
GMR HI Titer	2.01 (1.37, 2.96)	0.90 (0.62, 1.30)	1.79 (1.15, 2.79)	0.94 (0.61, 1.46)	1.43 (0.83, 2.44)	0.71 (0.42, 1.21)	4.44 (2.62, 7.55)	0.85 (0.51, 1.43)	32.55 (8.85, 119.71)	2.95 (0.78, 11.09)
SCR (%) HI Titer	24.11 (16.53, 33.10)	2.78 (0.58, 7.90)	13.08 (7.34, 20.98)	0.90 (0.02, 4.92)	9.91 (5.05, 17.04)	0.00 (NE, NE)	42.53 (31.99, 53.59)	3.53 (0.73, 9.97)	80.56 (71.83, 87.54)	8.33 (3.88, 15.23)

Source: Section 5.3.5.1, V130_14 CSR, Table 11-6.

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; GMR = geometric mean ratio; GMT = geometric mean titer; HI = hemagglutination inhibition; NA = not applicable (due to lack of agglutination of A/H3N2 in HI assay); NE = not estimable; NH = Northern Hemisphere; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SCR = seroconversion rate; SH = Southern Hemisphere.

Note 1: Season 1 = SH 2019; Season 2 = NH 2019/2020; Season 3 = NH 2020/2021; Season 4 = NH 2022/2023; Season 5 = SH 2023.

As indicated, the A/H3N2 strains for seasons 1 and 3 did not agglutinate red blood cells in the HI assay. This is due to recent evolutionary changes in the amino acids of the surface proteins hemagglutinin (HA) and neuraminidase (NA) of A/H3N2 viruses, resulting in a diminished capacity of HA to agglutinate target red blood cells in the HI assay. Thus, it is acceptable that for seasons 1 and 3, the Microneutralization assay is considered the primary immunogenicity assay.

Baseline HI GMT were variable across strain and season, but comparable in each of them between QIVc and the comparator vaccine groups.

Overall, QIVc was immunogenic across seasons eliciting highly variable HI responses with GMR in the range of 2.59-19.20 (A/H1N1), 1.81-7.43 (A/H3N2), 1.95-8.04 (B/Yamagata) and 1.43-32.55 (B/Victoria). Seroconversion rates were also variable, higher for A strains (A/H1N1: 29.89-75%; A/H3N2: 44.83-84.26%) than for B/strains (B/Yam: 23.42-66.67%; B/Vic: 9.91-80.56%).

For seasons 2 and 3, the results show low immunogenicity for B/Victoria strain: GMR were 1.79 and 1.43 (with 95% CI overlapping with the comparator vaccine), and seroconversion achieved only 13.08% and 9.91%, respectively.

Microneutralisation Assay

In addition to HI assays, MN assays were performed to measure antibody titers against the 4 QIVc strains in each vaccine group for the 5 study seasons.

Geometric Mean Titers

Day 1:

- For each of the 5 influenza seasons, the Day 1 MN GMTs were not notably different between the QIVc and comparator vaccine groups for any of the 4 vaccine strains (Table 10).
- The Day 1 MN GMT values varied across the 5 seasons for each strain.

Day 29/57:

- In the QIVc group, the Day 29/57 MN GMTs were observed to be higher than the Day 1 MN GMTs for each of the 4 vaccine strains across the 5 seasons, apart from the B/Victoria strain in Season 2, which was poorly immunogenic (Table 10).
- In the comparator vaccine group, the MN GMTs at Day 1 and Day 29/57 were not notably different for each of the 4 vaccine strains across the 5 seasons.
- The Day 29/57 MN GMTs were observed to be higher in the QIVc group compared with the comparator vaccine group for each of the 4 vaccine strains across the 5 seasons, apart from the B/Victoria strain in Season 2.

Geometric Mean Ratios

- For each of the 5 study seasons, the MN GMRs were observed to be higher in the QIVc group than in the comparator vaccine group for each of the 4 vaccine strains, apart from the B/Victoria strain in Season 2 (Table 11).

- In the QIVc group, the GMRs varied across the 5 seasons, with most variability observed in the GMR values for the A/H1N1 and B/Victoria strains.

- In the comparator vaccine group, there were no notable differences in GMRs across the 5 study seasons.

Seroconversion Rates

- For each of the 5 influenza seasons, the MN SCRs were observed to be higher in the QIVc group than in the comparator vaccine group for each of the 4 vaccine strains, apart from the B/Victoria strain in Season 2 (Table 10).

- In the QIVc group, the SCR for each vaccine strain varied across the 5 seasons.

Table 11 Pre- and Postvaccination GMT, GMR, and SCR in Subjects 6 Months Through 47 Months of Age (MN Assay Data) – As Randomized – FAS Immunogenicity, Study V130_14

Season	Season 1		Season 2		Season 3		Season 4		Season 5	
Any Strain	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)
A/H1N1	**N=112**	**N=108**	**N=107**	**N=111**	**N=111**	**N=112**	**N=87**	**N=85**	**N=108**	**N=108**
Day 1 MN GMT	22.06 (9.53, 51.07)	31.10 (13.83, 69.92)	57.54 (18.79, 176.16)	55.89 (18.69, 167.19)	61.40 (16.51, 228.37)	43.43 (11.93, 158.11)	32.15 (19.17, 53.90)	35.32 (21.25, 58.71)	113.94 (36.64, 354.34)	115.49 (36.41, 366.35)
Day 29/57 MN GMT	329.08 (196.16, 552.06)	36.24 (21.97, 59.79)	473.15 (247.69, 903.85)	66.69 (35.39, 125.71)	459.87 (157.55, 1342.31)	19.32 (6.76, 55.21)	86.91 (58.51, 129.11)	46.51 (31.53, 68.60)	352.09 (110.01, 1126.90)	86.61 (26.51, 282.92)
GMR MN Titer	16.16 (9.52, 27.45)	1.70 (1.02, 2.83)	8.12 (4.19, 15.75)	1.15 (0.60, 2.20)	17.55 (5.72, 53.86)	0.81 (0.27, 2.44)	2.37 (1.54, 3.67)	1.23 (0.80, 1.88)	3.47 (1.07, 11.24)	0.85 (0.26, 2.81)
SCR (%) MN Titer	73.21 (64.02, 81.14)	2.78 (0.58, 7.90)	74.77 (65.45, 82.67)	4.50 (1.48, 10.20)	87.39 (79.74, 92.93)	4.46 (1.47, 10.11)	32.18 (22.56, 43.06)	7.06 (2.63, 14.73)	68.52 (58.88, 77.12)	15.74 (9.45, 24.00)
A/H3N2	**N=112**	**N=108**	**N=107**	**N=111**	**N=111**	**N=112**	**N=87**	**N=85**	**N=108**	**N=108**
Day 1 MN GMT	6.92 (4.91, 9.76)	6.29 (4.51, 8.76)	4.96 (4.19, 5.88)	4.80 (4.07, 5.67)	7.02 (3.18, 15.51)	8.33 (3.82, 18.16)	17.70 (10.34, 30.31)	15.77 (9.29, 26.76)	26.08 (7.79, 87.37)	25.98 (7.59, 88.87)
Day 29/57 MN GMT	27.55 (18.70, 40.58)	10.95 (7.52, 15.94)	12.04 (7.60, 19.08)	5.31 (3.38, 8.34)	57.93 (28.43, 118.06)	10.49 (5.21, 21.09)	35.99 (18.52, 69.94)	14.78 (7.70, 28.34)	139.97 (41.52, 471.84)	30.22 (8.78, 104.08)
GMR MN Titer	3.28 (2.23, 4.84)	1.32 (0.91, 1.92)	2.14 (1.35, 3.40)	0.93 (0.59, 1.46)	5.92 (2.79, 12.56)	1.01 (0.48, 2.13)	2.74 (1.39, 5.38)	1.16 (0.60, 2.26)	4.40 (1.30, 14.88)	0.95 (0.27, 3.28)
SCR (%) MN Titer	38.39 (29.36, 48.06)	4.63 (1.52, 10.47)	20.56 (13.36, 29.46)	1.80 (0.22, 6.36)	57.66 (47.92, 66.98)	1.79 (0.22, 6.30)	33.33 (23.58, 44.25)	10.59 (4.96, 19.15)	71.30 (61.80, 79.59)	15.74 (9.45, 24.00)
B/Yamagata	**N=112**	**N=108**	**N=107**	**N=111**	**N=111**	**N=112**	**N=87**	**N=85**	**N=108**	**N=108**
Day 1 MN GMT	76.91 (53.50, 110.55)	66.14 (46.60, 93.87)	65.25 (35.87, 118.70)	60.03 (33.41, 107.86)	15.33 (7.73, 30.41)	15.26 (7.78, 29.93)	53.41 (32.42, 88.00)	54.11 (33.12, 88.41)	51.81 (23.27, 115.35)	45.20 (20.02, 102.06)
Day 29/57 MN GMT	278.89 (202.31, 384.46)	88.67 (65.06, 120.84)	283.42 (183.07, 438.79)	126.59 (82.43, 194.41)	55.17 (27.19, 111.92)	19.24 (9.59, 38.59)	84.60 (55.74, 128.38)	52.11 (34.57, 78.55)	169.24 (75.01, 381.86)	49.34 (21.58, 112.85)
GMR MN Titer	3.93 (2.81, 5.49)	1.30 (0.94, 1.79)	3.05 (1.95, 4.75)	1.38 (0.89, 2.13)	3.15 (1.47, 6.71)	1.10 (0.52, 2.32)	1.82 (1.15, 2.88)	1.11 (0.71, 1.75)	3.81 (1.56, 9.33)	1.19 (0.48, 2.95)
SCR (%) MN Titer	46.43 (36.95, 56.10)	0.93 (0.02, 5.05)	30.84 (22.27, 40.50)	3.60 (0.99, 8.97)	36.94 (27.97, 46.62)	4.46 (1.47, 10.11)	19.54 (11.81, 29.43)	4.71 (1.30, 11.61)	54.63 (44.76, 64.24)	7.41 (3.25, 14.07)
B/Victoria	**N=112**	**N=108**	**N=107**	**N=111**	**N=111**	**N=112**	**N=87**	**N=85**	**N=108**	**N=108**
Day 1 MN GMT	6.07 (4.82, 7.65)	6.64 (5.31, 8.30)	4.99 (4.16, 5.99)	5.18 (4.33, 6.18)	9.09 (4.80, 17.24)	10.71 (5.71, 20.09)	8.79 (6.40, 12.07)	7.72 (5.66, 10.55)	15.97 (2.53, 100.98)	12.20 (1.87, 79.68)
Day 29/57 MN GMT	14.23 (10.95, 18.51)	7.00 (5.44, 9.02)	5.29 (4.03, 6.92)	5.26 (4.04, 6.85)	26.81 (14.06, 51.12)	9.65 (5.12, 18.20)	121.02 (59.56, 245.87)	5.99 (2.99, 11.97)	938.65 (230.67, 3819.51)	39.32 (9.41, 164.32)
GMR MN Titer	2.17 (1.67, 2.82)	1.07 (0.83, 1.37)	1.04 (0.77, 1.40)	1.01 (0.75, 1.35)	2.74 (1.37, 5.47)	0.92 (0.47, 1.83)	16.90 (8.36, 34.19)	0.86 (0.43, 1.72)	31.51 (7.19, 138.05)	1.42 (0.31, 6.37)

Season	Season 1		Season 2		Season 3		Season 4		Season 5	
Any Strain	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)	QIVc No. or % (95% CI)	Comparator No. or % (95% CI)
SCR (%)	20.54	0.93	0.93	2.70	25.23	0.89	87.36	7.06	94.44	9.26
MN Titer	(13.49, 29.20)	(0.02, 5.05)	(0.02, 5.10)	(0.56, 7.70)	(17.46, 34.35)	(0.02, 4.87)	(78.50, 93.52)	(2.63, 14.73)	(88.30, 97.93)	(4.53, 16.37)

Source: Section 5.3.5.1, V130_14 CSR, Table 11-7.

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; GMR = geometric mean ratio; GMT = geometric mean titer; MN = microneutralization; NH = Northern Hemisphere; QIVc = cell-based quadrivalent subunit influenza virus vaccine; SCR = seroconversion rate; SH = Southern Hemisphere.

Note 1: Season 1 = SH 2019; Season 2 = NH 2019/2020; Season 3 = NH 2020/2021; Season 4 = NH 2022/2023; Season 5 = SH 2023.

Baseline MN GMT were variable across strain and season, but comparable in each of them between QIVc and the comparator vaccine groups.

Overall, QIVc elicited a neutralizing antibody response for the four strains across the 5 seasons, with the exception of B/Victoria strain during Season 2, when no rise in antibody titres was detected (GMR: 1.04) and there was no seroconversion (0.93%). As mentioned before, there was also low immunogenicity for this strain and season in terms of HI antibodies. Furthermore, during this and the previous season, a lack of efficacy was observed for B/Victoria. It was noticed the poor immunogenicity and apparent lack of efficacy for B/Victoria during Seasons 1 and 2. According to the MAH, this study was not designed to evaluate the association of the magnitude of immune responses to prevention of influenza. The intent of the immunogenicity subset was to evaluate, for each season, evidence of an immune response to the QIVc vaccine. As observed, HI and MN antibody responses to the B/Victoria vaccine strain were less immunogenic in seasons 1 and 2 than for later seasons. The mismatch for the B/Victoria vaccine strain to circulating virus in seasons 1 and 2 complicates the ability to derive an association of immunogenicity with efficacy. This is acknowledged.

Other than season 2, the MN antibody response was highly variable across seasons, with GMR in the range of 2.37-17.55 (A/H1N1), 2.14-5.92 (A/H3N2), 1.82-3.93 (B/Yamagata) and 2.17-31.51 (B/Victoria). Seroconversion rates were also variable and in the range of 32.18-87.39% (A/H1N1), 20.56-71.30% (A/H3N2), 19.54-54.63% (B/Yamagata) and 20.54-94.44% (B/Victoria).

Ancillary analyses

The efficacy subgroup analyses were stratified by age (6 months through 23 months; 24 months through 47 months); influenza vaccination history (Yes; No); race; sex; country of enrolment; and season/year of study participation. The immunogenicity subgroup analyses were stratified by age (6 months through 23 months; 24 months through 47 months); prevaccination titer (<1:10; ≥1:10); influenza vaccination history (Yes; No); race; sex; and country.

The efficacy and immunogenicity subgroup analyses were not powered for hypothesis testing and, therefore, descriptive efficacy results in subgroups with a small sample size or few influenza events should be interpreted with caution. The vaccine efficacy confidence interval is to be interpreted with caution for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis or when vaccine efficacy was estimated as 100% on the basis of zero cases. The immunogenicity analyses were conducted in a subset of subjects and presented by season; therefore, the number of subjects in some

subgroup analyses was very small and the data were insufficient to provide results for the immunogenicity endpoints.

All subgroup analyses presented in this section have been performed using the FAS Efficacy/Immunogenicity.

Comparison of Efficacy Results in Subpopulations

Efficacy Results by Age

The aVE point estimate for QIVc versus the comparator vaccine was positive in both the 6 months through 23 months and the 24 months through 47 months age subgroups. A higher point estimate was observed in the older age subgroup compared with the younger age subgroup for both RT-PCR confirmed influenza due to any strain (47.24%, 95% CI: 26.62, 62.06 vs 32.77%, 95% CI: 3.22, 53.29) and culture confirmed influenza due to matched strains (54.29%, 95% CI: 24.20, 72.43 vs 36.60%, 95% CI: -8.56, 62.98); the 95% CIs observed for the younger age subgroup were wide as there were fewer cases compared with the older age subgroup.

A similar pattern of a higher point estimate for aVE in the older age subgroup than the younger age subgroup was observed for culture confirmed influenza due to unmatched strains and culture confirmed influenza due to any strain.

Efficacy Results by Influenza Vaccination History

Of the 5691 subjects in the FAS Efficacy, only 110 subjects were previously vaccinated against influenza. In total, there were only 6 cases of RT-PCR confirmed influenza (any strain) and 4 cases of culture confirmed influenza in this subgroup, and no firm interpretation could be made. Given that the majority of subjects in the study were not previously vaccinated, the aVEs for RT-PCR confirmed influenza (any strain) and culture confirmed influenza (matched strain, unmatched strain, any strain) for these subjects were not notably different from the corresponding aVEs reported in the overall study population.

Efficacy Results by Race

There was only 1 subject in the Native Hawaiian or Other Pacific Islander subgroup (in the comparator vaccine group); this subject did not have a confirmed case of influenza. There were too few cases of confirmed influenza in the Black or African American subgroup to estimate aVE. The point estimates of aVE for QIVc versus the comparator vaccine were positive, albeit varied, for the Asian, White, and Other subgroups for RT-PCR confirmed influenza (any strain) and culture confirmed influenza (matched strain, unmatched strain, any strain), with wide 95% CIs observed for the White and Other subgroups, which had fewer cases than the Asian subgroup. The Asian subgroup had aVE point estimates of 57.25% (95% CI: 36.33, 71.30), 55.93% (95% CI: 26.21, 73.67), 73.47% (95% CI: 19.95, 91,21), and 62.88% (95% CI: 39.99, 77.05) for RT-PCR confirmed influenza (any strain) and culture confirmed influenza (matched strain, unmatched strain, any strain), respectively.

Efficacy Results by Sex

The point estimates of aVE for QIVc versus the comparator vaccine were positive for both the male and female subgroups, as assessed by RT-PCR confirmed influenza (any strain) and cultured confirmed influenza (matched strain, unmatched strain, any strain). The point estimates of aVE for the female subgroup were similar to or lower than those in the male subgroup, with more variable and wider 95% CI observed with the female subgroup.

Efficacy Results by Country

Of the 15 countries that participated in the study, 3 countries (Latvia, New Zealand, and Romania) had no RT-PCR confirmed influenza cases. Nine countries had 14 or fewer RT-PCR confirmed influenza cases; no firm conclusions were able to be made regarding the aVE of QIVc versus the comparator vaccine. For the countries of Estonia, Honduras, and Philippines, 38, 85, and 88 RT-PCR confirmed cases (any strain), respectively, were observed; the point estimates of aVE were 50.13% (95% CI: 2.01, 74.62), 21.31% (95% CI: -20.68, 48.69); and 61.63% (95% CI: 38.97, 75.87), respectively. For culture confirmed influenza due to matched strains, the point estimates of aVE were 51.68% (95% CI: 42.43, 83.61), 50.66% (95% CI: -9.82, 77.83), and 54.44% (95% CI: 17.46, 74.85), respectively. The point estimates of aVE for QIVc versus the comparator vaccine were also positive for these 3 countries for culture confirmed influenza due to unmatched strains or any strain, with wide 95% CIs for Honduras and Estonia.

Efficacy Results by Season

The point estimates of aVE for QIVc versus the comparator vaccine varied across the 5 seasons of the study for RT-PCR confirmed influenza (any strain) and culture confirmed influenza (matched strain, unmatched strain, any strain) as the number and distribution of cases varied by season (Table 12). Surveillance for influenza cases was curtailed for the NH 2019/2020 season (Season 2), due to the declaration by the WHO of a pandemic with SARS-CoV-2 in March 2020. For the NH 2020/2021 season (Season 3), a total of 5 influenza cases was observed and aVE of QIVc versus the comparator vaccine could not be determined. The fourth study season was conducted during the NH 2022/2023 influenza season, when global surveillance indicated a return in influenza activity, although not to pre-pandemic levels. Robust point estimates of aVE for QIVc versus the comparator vaccine were observed in Season 4 and Season 5 (SH 2023) for RT-PCR confirmed influenza due to any strain (Season 4: 54.54%, 95% CI: 2.74, 78.75; Season 5: 61.69%, 95% CI: 36.46, 76.91), culture confirmed influenza due to matched strains (Season 4: 66.79%, 96% CI: -3.53, 89.35; Season 5: 58.15%, 95% CI: 23.31, 77.16), and culture confirmed influenza due to any strain (Season 4: 65.03%, 95% CI: 10.81, 86.29; Season 5: 66.90%, 95% CI: 40.49, 81.59) (Table 12).

Table 12 Number of Subjects with First-Occurrence RT-PCR Confirmed Influenza, Number of Subjects with First Occurrence Culture Confirmed Influenza (Matched Strain, Unmatched Strain, Any Strain) and Absolute Vaccine Efficacy in Subjects 6 Months Through 47 Months of Age by Season – As Randomized – FAS Efficacy, Study V130_14

Season	Season 1		Season 2		Season 3		Season 4		Season 5	
	QIVc N=344	Comparator N=347	QIVc N=495	Comparator N=484	QIVc N=523	Comparator N=518	QIVc N=496	Comparator N=501	QIVc N=998	Comparator N=985
RT-PCR confirmed influenza – Any strain[a]										
No. of cases (attack rate)	55 (15.99)	74 (21.33)	16 (3.23)	22 (4.55)	2 (0.38)	3 (0.58)	10 (2.02)	21 (4.19)	21 (2.10)	53 (5.38)
aVE%[b] (95% CI)	26.15 (-4.83, 47.98)		29.43 (-34.43, 62.95)		33.38 (-298.71, 88.87)		54.54 (2.74, 78.75)		61.69 (36.46, 76.91)	
Culture confirmed influenza – Matched strain[c]										
No. of cases (attack rate)	18 (5.23)	29 (8.36)	7 (1.41)	6 (1.24)	0 (0)	0 (0)	4 (0.81)	12 (2.40)	15 (1.50)	35 (3.55)
aVE%[b] (95% CI)	37.14 (-13.29, 65.13)		-13.59 (-238.20, 61.85)		NE (NE, NE)		66.79 (-3.53, 89.35)		58.15 (23.31, 77.16)	

Culture confirmed influenza – Unmatched strain[d]										
No. of cases (attack rate)	14 (4.07)	22 (6.34)	4 (0.81)	7 (1.45)	0 (0)	0 (0)	2 (0.40)	5 (1.00)	0 (0)	9 (0.91)
aVE%[b] (95% CI)	36.96 (-23.32, 67.78)		46.94 (-81.83, 84.51)		NE (NE, NE)		59.24 (-111.13, 92.13)		100 (100, 100)	
Culture confirmed influenza – Any strain[e]										
No. of cases (attack rate)	29 (8.43)	48 (13.83)	11 (2.22)	12 (2.48)	0 (0)	0 (0)	6 (1.21)	17 (3.39)	15 (1.50)	44 (4.47)
aVE%[b] (95% CI)	39.93 (4.63, 62.17)		12.72 (-98.11, 61.55)		NE (NE, NE)		65.03 (10.81, 86.29)		66.90 (40.49, 81.59)	

Source: Section 5.3.5.1, V130_14 CSR, Table 14.2.1.1.13, Table 14.2.2.1.13, Table 14.2.3.1.13, and Table 14.2.3.2.13.

Abbreviations: aVE = absolute efficacy; CI = confidence interval; FAS = Full Analysis Set; NE = not estimable; NH = Northern Hemisphere; QIVc = cell-based quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription-polymerase chain reaction; SH = Southern Hemisphere.

[a] RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine occurring at >14 days after the last vaccination in the treatment period until the end of the influenza season, in association with protocol-defined ILI symptoms.

[b] Adjusted aVE, estimated from a Cox proportional hazard model for time from >14 days after the last study vaccination to the onset of the first occurrence of RT-PCR confirmed influenza or culture confirmed influenza (matched strain, unmatched strain, any strain) with vaccine group as the main effect, adjusting for age group, previous vaccination status, sex, and country as random effects. Note that the age group is from planned stratification.

[c] Culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to the influenza strains selected for the seasonal influenza vaccine occurring at >14 days after the last vaccination in the treatment period until the end of the influenza season, in association with protocol-defined ILI symptoms.

[d] Culture confirmed influenza due to influenza Type A and/or Type B virus antigenically unmatched to the influenza strains selected for the seasonal influenza vaccine occurring at >14 days after the last vaccination until the end of the influenza season, in association with protocol-defined ILI symptoms.

[e] Culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine occurring at >14 days after the last vaccination until the end of the influenza season, in association with protocol-defined ILI symptoms.

Note 1: Season 1 = SH 2019; Season 2 = NH 2019/2020; Season 3 = NH 2020/2021; Season 4 = NH 2022/2023; Season 5 = SH 2023.

aVE analysis was also performed in different subgroups: age, vaccination history, race, sex, country and season. These analyses were not powered for hypothesis testing and therefore are descriptive results with wide confidence intervals in some cases. None of these analyses questioned the superior aVE of the QIVc vs the comparator.

Regarding the two age groups, a higher point estimate was observed in the older age subgroup compared with the younger age subgroup for both RT-PCR confirmed influenza due to any strain (47.24%, 95% CI: 26.62, 62.06 vs 32.77%, 95% CI: 3.22, 53.29) and culture confirmed influenza due to matched strains (54.29%, 95% CI: 24.20, 72.43 vs 36.60%, 95% CI: -8.56, 62.98). This result is consistent with previous results in other clinical studies carried out with this vaccine and is probably related to the weaker immune response in influenza naïve individuals, which are usually more abundant in the younger age group.

Of the 5691 subjects in the FAS Efficacy, only 110 subjects were previously vaccinated against influenza. In total, there were only 6 cases of RT-PCR confirmed influenza (any strain) and 4 cases of culture confirmed influenza in this subgroup, and no firm interpretation could be made.

In the subgroups by race, only robust results were obtained for some races. The Asian population was the most numerous, and had aVE point estimates consistent with the results obtained in the overall population.

In the same way, subgroup analysis by sex was also positive in both subpopulations and in line with the general aVE results.

The results obtained by country were very variable, nine (out of 15) countries had 14 or less RT-PCR confirmed influenza cases and no firm conclusions could be made. There were three countries in which a robust aVE analysis could be made, and the results are positive and similar as the other obtained point estimates.

Regarding the study seasons, the number and distribution of cases varied by season. Moreover, the surveillance in the NH 2020/2021 season yielded few influenza cases due to the pandemic declaration in March 2020. Robust point estimates of aVE for QIVc were observed in season 4 and 5 and were in line with the rest of the results.

In the efficacy analysis by season and strain (CSR – Table 14.2.1.1.13), it is noted that during seasons 1 and 2 (SH19 and NH19/20) there was apparently no efficacy for RT-PCR confirmed Influenza cases due to B strains: For season 1 there were 21 cases in QIVc group vs 22 in the Comparator group, while for season 2 there were 6 cases in each group. This was mostly due to an apparent lack of efficacy for B/Victoria strain: 17 cases in each group during Season 1, and 5 cases (QIVc) vs 3 cases (Comparator) during Season 2. During both seasons, the B/Victoria strain was the same.

Overall, the data and analysis are considered adequate.

Comparison of Immunogenicity Results in Subpopulations

Immune responses at Day 29/57 were not evident in the comparator vaccine group, as assessed by both the HI and MN assays; therefore, the observations below are focused on the immunogenicity subgroup analyses for the QIVc group only.

Immunogenicity Results by Age

Immune responses were observed in both the 6 months through 23 months age subgroup and the 24 months through 47 months age subgroup, with the Day 29/57 GMTs observed to be higher than the Day 1 GMTs for the 4 vaccine strains. Day 29/57 GMTs in the 24 months through 47 months age subgroup were similar to or higher than those in the 6 months through 23 months age subgroup in each of the 5 influenza seasons, as assessed by both the HI and MN assays.

In general, the HI and MN GMRs in the 24 months through 47 months age subgroup were observed to be similar to or higher than those in the 6 months through 23 months age subgroup for the 4 vaccine strains in each study season.

Immunogenicity Results by Prevaccination Titer

Per the definition for this subgroup, Day 1 GMTs were different between subjects with prevaccination titer <1:10 and those with prevaccination titer ≥1:10. For both subgroups, the Day 29/57 GMTs were observed to be higher than the Day 1 GMTs for the 4 vaccine strains for each of the 5 seasons, as assessed by both the HI and MN assays.

In general, the HI and MN GMRs were observed to be higher in subjects with prevaccination titer <1:10 than those in subjects prevaccination titer ≥1:10 for the A/H1N1 and A/H3N2 strains; the HI and MN GMRs were more variable between the 2 subgroups for the B/Yamagata and B/Victoria strains.

Immunogenicity Results by Influenza Vaccination History

Due to the very small number of previously vaccinated subjects in the QIVc group in the FAS Immunogenicity (12 subjects across the 5 seasons), no conclusions could be drawn for this subgroup. For the subgroup of not previously vaccinated subjects, which included the majority of subjects enrolled in

the FAS Immunogenicity, immune responses were evident for each vaccine strain for the 5 study seasons, with variability observed across the seasons, most notably the GMRs for the A/H1N1 and B/Victoria strains.

Immunogenicity Results by Race

Excluding the seasons where ≤5 subjects were included from a race category, Asian subjects were included in the FAS Immunogenicity in Seasons 1 and 5, Black or African American subjects in Season 5, White subjects in Seasons 2, 3 and 4, and subjects in the other race category were included in the FAS Immunogenicity in Seasons 1 and 5.

Immune responses were evident in the racial subgroups, where applicable, as assessed by both the HI and MN assays. Comparisons between the race subgroups are limited by the small sizes of the subgroups and the differences in percentages of the race subgroup in the immunogenicity subset within an influenza season.

Immunogenicity Results by Sex

For both the male and female subgroups, the results were consistent with the overall study results, with the Day 29/57 GMTs observed to be higher than the Day 1 GMTs for each of the 4 vaccine strains across the 5 seasons, as assessed by the HI and MN assays.

There were no notable differences in the HI and MN GMRs for the 4 vaccine strains between the male and female subgroups.

Immunogenicity Results by Country

In total, 7 countries provided subjects for the FAS Immunogenicity (Season 1: Honduras, Malaysia, Philippines, and Thailand; Season 2: Estonia and Poland; Season 3: Estonia; Season 4: Estonia and Poland; Season 5: Philippines and South Africa).

Immune responses were evident in each of the countries, as assessed by both the HI and MN assays, with variability in GMRs for the 4 strains by country and by season. Comparisons between countries are limited by the small number of subjects enrolled in the subset from some of the countries and the different seasons in which these countries were part of the immunogenicity subset for the study.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13 Summary of Efficacy for trial V130_14

A Phase III, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine When Administrated in Healthy Subjects Aged 6 Months Through 47 Months	
Study identifier	V130_14

Design	Randomized, Observer Blind, Multicenter	
	Duration of main phase:	Day 1 (vaccination) through Day 29 (previously vaccinated subjects receiving a single dose of study vaccine) or Day 57 (not previously vaccinated subjects receiving 2 doses of study vaccine)
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	
Treatments groups	Vaccine group: QIVc	Season 1 [Southern Hemisphere 2019]: Strain Type A/Singapore/GP1908/2015 IVR-180 (A/H1N1) Strain Type A/North Carolina/04/2016 (A/H3N2) Strain Type B/Singapore/INFTT-16-0610/2016 (B/Yamagata) Strain Type B/Iowa/06/2017 (B/Victoria) Season 2 [Northern Hemisphere 2019-2020]: Strain Type A/Idaho/07/2018 (A/H1N1) Strain Type A/Indiana/08/2018 (A/H3N2) Strain Type B/Singapore/INFTT-16-0610/2016 (B/Yamagata) Strain Type B/Iowa/06/2017 (B/Victoria) Season 3 [Northern Hemisphere 2020-2021]: Strain Type A/Nebraska/14/2019 (A/H1N1) Strain Type A/Delaware/39/2019 (A/H3N2) Strain Type B/Singapore/INFTT-16-0610/2016 (B/Yamagata) Strain Type B/Darwin/7/2019 (B/Victoria) Season 4 [Northern Hemisphere 2022-2023]: Strain Type A/Delaware/55/2019 CVR-45 (A/H1N1) Strain Type A/Darwin/11/2021 (A/H3N2) Strain Type B/Singapore/INFTT-16-0610/2016 (B/Yamagata) Strain Type B/Singapore/WUH4618/2021 (B/Victoria) Season 5 [Southern Hemisphere 2023]: Strain Type A/Sydney/5/2021 CVR-115 (A/H1N1) Strain Type A/Darwin/11/2021 (A/H3N2) Strain Type B/Singapore/INFTT-16-0610/2016 (B/Yamagata) Strain Type B/Singapore/WUH4618/2021 (B/Victoria) One or two doses depending on previous influenza vaccine status.
	Comparator: Non-Influenza Vaccine	Meningococcal group C polysaccharide conjugate vaccine (MenC)
	Placebo	Sodium Chloride Injection 0.9% w/v

Endpoints and definitions	Primary endpoint	Efficacy in preventing confirmed influenza cases	This endpoint was met if the lower limit (LL) of the two-sided 97.5% confidence interval (CI) of the absolute vaccine efficacy (aVE) estimate was greater than 0% (primary objective) in at least one of the two primary efficacy endpoints. Using confirmed influenza cases assessed from > 14 days after the last vaccination and until the end of the influenza season. The cases were confirmed either by RT-PCR (primary endpoint 1a) or by culture (primary endpoint 1b) for the entire age range (6 months through 47 months of age).
	Secondary endpoints	Efficacy in preventing confirmed influenza cases	For secondary objective 1: Culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza 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: Culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season. For secondary objective 3: RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season.
Database lock	February 13th 2024		

Results and Analysis

Analysis description	**Primary Analysis, Efficacy in preventing confirmed influenza cases**			
Analysis population and time point description	final analysis			
Descriptive statistics and estimate variability	Treatment group	Vaccine group	Comparator group	aVE (CI %)
	Number of subjects	2856	2835	
Primary endpoints	RT-PCR confirmed influenza Antigenically matched culture confirmed influenza Number of cases (attack rate)	104 (3.64) 44 (1.54)	173 (6.10) 82 (2.89)	41.26 (97.98% CI:21.55, 56.02) 46.90 (97.5% CI: 19.19, 65.11)

----------	Culture confirmed influenza – Unmatched strains	20 (0.70)	43 (1.52)	54.49 (95% CI: 22.55, 73.26)
Secondary endpoints	Culture confirmed influenza - Any strain	61 (2.14)	121 (4.27)	50.67 (95% CI: 32.83, 63.77)
	RT-PCR confirmed moderate-to-severe influenza Number of cases (attack rate)	0	9 (0.32)	100 (95% CI: NE, 100)

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study V130_14 was a Phase 3, randomized, observer-blind, comparator-controlled, multicenter study to evaluate the efficacy, immunogenicity, and safety of QIVc versus a non-influenza vaccine (meningococcal group C polysaccharide conjugate vaccine [MenC vaccine]; NeisVac-C) in children 6 months through 47 months of age. The study was conducted over 5 influenza seasons (Southern Hemisphere [SH] 2019, Northern Hemisphere [NH] 2019/2020, NH 2020/2021, NH 2022/2023, and SH 2023).

No dose-finding studies were conducted since the vaccine composition and dosing are based on the Guideline on Influenza vaccines – Quality module (EMA/CHMP/BWP/310834/2012 Rev.1), and the vaccine compositions are in line with the antigen dose of other seasonal inactivated non-adjuvanted influenza vaccines. Thus, it is agreed that it was not needed to perform dose-response studies.

The case definition of ILI for this study (a temperature ≥37.8°C (≥100.0°F) and at least one of the following symptoms on the same day: cough, sore throat, nasal congestion, rhinorrhoea, earache or ear discharge) as well as the case definition for moderate-to-severe ILI are considered adequate.

The management of the nasopharyngeal swabs, the RT-PCR confirmation and the cell culture activities for strain subtype determination are endorsed. The table that details the route of swab collection (Table 11-1 in the CSR) has three items: nasopharyngeal, oropharyngeal and other. The sum of the three percentages is not equal to 100%. The MAH indicated that there were two reasons to explain why the sum of the percentages for nasopharyngeal, oropharyngeal, and other swab types was not equal to 100%. The first reason was that the percentages for each route of collection use the total N from the 'Collection of swab for ILIs reported >14 days after last vaccination to end of influenza season' and the second one was that a single influenza-like illness (ILI) could involve the collection of swabs from multiple routes.

The use of HI and MN assays to describe immunogenicity is according to the CHMP Guideline on influenza vaccines – Non-clinical and clinical module. The Cell Mediated Immunity (CMI) was not measured in this study because CMI response to QIVc vaccine in young children was previously evaluated in study V130_10.

The total number of study participants is considered appropriate to demonstrate absolute vaccine efficacy.

The inclusion/exclusion criteria are considered satisfactory.

Moreover, the strain composition of the vaccine met the WHO and CHMP recommendations for the seasons in which the CT were performed. Therefore, this is considered adequate too.

All objectives are considered acceptable. Particularly, it is important to note that the primary endpoint is aimed at demonstrating clinical efficacy in terms of disease prevention.

The primary objective is made of two parts, and the objective would be met if at least one of the two parts is achieved. One of the parts is to demonstrate efficacy of QIVc against RT-PCR confirmed ILI cases regardless of antigenic match and the other to demonstrate vaccine efficacy against culture confirmed illness caused by influenza virus strains antigenically matched to the vaccine composition. This approach is found to be sensible. An estimation of efficacy against influenza due to strains that are well-matched or unmatched (RT-PCR or culture confirmed) to those in the vaccine was analysed. This is considered important to show the overall potential benefit of the vaccine.

The secondary efficacy objectives are agreed upon, especially the prevention of culture confirmed illness caused by any influenza type A and/or type B virus and the prevention of RT-PCR confirmed moderate-to-severe illness caused by any influenza type A and/or type B virus. The third secondary objective, the prevention of culture conformed illness caused by influenza virus strains antigenically dissimilar to the vaccine composition, has been evaluated for completeness and as a way of complementing the information on VE coming from the antigenically matched strains.

The efficacy endpoint definitions followed the EU guidance, so they are considered adequate. An ILI case was defined as body temperature of ≥100.0°F/ ≥37.8°C (i.e., fever) along with any of the following symptoms: cough, sore throat, nasal congestion, rhinorrhoea, earache or ear discharge. This ILI definition goes along with the guideline on Influenza vaccines (EMA/CHMP/VWP/457259/2014) recommendations and take into account the ECDC European Centre for Disease Prevention and Control (ECDC) definitions for ILI. The Influenza case definition was also properly defined following also de EU recommendations.

The sample size calculations in order to have at least 90% power to demonstrate QIVc vaccine efficacy are considered adequate.

Subjects were randomized in a 1:1 ratio to receive QIVc or the non-influenza vaccine comparator (meningococcal group C polysaccharide conjugate vaccine [MenC vaccine]; NeisVac-C). Randomisation was stratified by age (6 through 23 months and 24 through 47 months) and by influenza vaccination history. Both types of stratification are sensible taking into account the study population, which is composed of very young children that will most likely present diverse immune responses determined by their age and also influenced by whether they have been previously vaccinated against influenza. It was determined that at least 30% of the participants had to be in each of the two age groups, this is acknowledged and agreed.

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 and therefore acceptable.

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 it is very unlikely that this design would have affected the study outcomes.

The statistical methods are overall considered adequate. In study V130_14 the primary objective of efficacy was achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints, that is, if the lower limit (LL) of the two-sided 97.5% CI of VE was greater than 0% in subjects 6 months through 47 months of age. 0% is very low having in mind that for instance, in study V130_12, which supported the extension of indication from 9 years and above to 2 years and above, as well as in supporting clinical studies for other authorised flu vaccines in children aged from 6 to 35 months, the LL of the 2-sided CI of the VE estimate, with at least 95% coverage was higher than 20%. The MAH indicated that study V130_14 started before the results of study V130_12 were known (in which the LL of the CI for aVE was >20% for subjects 2 to <18 years); that study V130_14 had majority of subjects that were not previously vaccinated and

were below 2 years of age, so the response of the children in study V130_14 was expected to be lower than in study V130_12; and that the lower bound of the VE for study V130_14 was agreed by the PDCO and also supported by interactions with regulatory agencies. Therefore, the LL for the CI of the VE criterion is considered sufficiently justified.

A total of 5723 study participants were enrolled in the study. There were only 2.8% of subjects who discontinued the study, and this is considered acceptable. Nevertheless, it is noted that the number of subjects that did not receive any study vaccine at all is significantly higher for the Comparator than for the QIVc group: 21 (0.7%) vs 2 (0.1%). The MAH explained that the main reason for the imbalance between groups was due to an insufficient supply of the comparator vaccine. The baseline characteristics of the enrolled subjects were well balanced between treatment groups. The planned age distribution of at least 30% of subjects in each age subgroup was achieved: 44.2% of subjects were 23 months of age or younger and 55.8% of subjects were 24 months of age or older. Only 1.9% of the subjects had been previously vaccinated against influenza and received 1 dose of study vaccine. Therefore, 98.1% received 2 vaccine doses. This very high proportion of non-previously vaccinated participants reflects the very low influenza vaccination that takes place in this age group. All other baseline and demographic characteristics are well balanced between the QIVc and the comparator group. There are some races and ethnic origins that are more represented than others but is this not expected to impact in the study results. For instance, it is noted that more than half of the participants in the FAS Immunogenicity set are Estonian. Nevertheless, it is not expected to have an impact on the immunogenicity results.

Efficacy objectives were assessed in the FAS efficacy population, instead of in the PPS (Per Protocol Set). It is observed that there is around a 10% difference between the FAS and the PPS populations (for the FAS efficacy, n=2856 (99.9%) in QIVc and n=2835 (99.0%) in the comparator whereas in the PPS n=2573 (90.0%) in QIVc and n=2531 (88.4%) in the comparator. Moreover, the PPS excludes all participants that have been excluded because of protocol deviations or other reasons. The MAH submitted within this procedure the results of the efficacy analyses of the primary endpoints in both the FAS and PPS populations and they were similar. In addition, the choice of the FAS population is consistent with the ICH E9. Therefore, the use of the FAS population to assess efficacy is endorsed.

Efficacy data and additional analyses

The study protocol included the possibility to conduct an interim analysis when a certain number of PCR-confirmed ILIs were achieved. This took place after Season 3 of the study. In order to maintain the overall alpha of 1.25% (one-sided), the CIs for the aVE estimate associated with the primary efficacy objectives were to be adjusted. The CI for primary efficacy endpoint 1a was adjusted from 97.5% to 97.98%, and the CI for primary efficacy endpoint 1b remained at 97.5%. The MAH presented the information fractions used in the cumulative O'Brien-Fleming type error-spending-function and the calculations for the adjustments of the CI for primary endpoints 1a and 1b in the final analysis and it was adequately justified the reason for adjusting only 1a and not both.

Both pre-specified success criteria for the primary endpoints 1a and 1b were met, so absolute vaccine efficacy (aVE) was demonstrated for QIVc versus the non-influenza comparator vaccine. The primary objective of efficacy was considered to be achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints. Both primary efficacy endpoints met the success criteria, therefore the primary objective of the study was achieved. For RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 41.26% (97.98% CI: 21.55, 56.02). For culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to vaccine strain the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 46.90% (97.5% CI: 19.19, 65.11).

The primary efficacy results in the PPS Efficacy population were consistent with the previously shown results (from the FAS Efficacy).

The secondary objectives, culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza strains in the vaccine, culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match and RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match, were also met.

For first occurrence of culture confirmed influenza due to influenza virus strains that were antigenically dissimilar to the vaccine strains (ie, unmatched strains), the aVE observed was 54.49% (95% CI: 22.55, 73.26). For first occurrence of culture confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strains, the aVE was 50.67% (95% CI: 32.83, 63.77). For first occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, there were 0 cases in the QIVc group and 9 cases in the comparator vaccine group. The aVE point was 100%; however, because of the low numbers, results must be taken with caution.

Interestingly, the point estimate for aVE for culture confirmed influenza due to strains dissimilar to those in the vaccine (was 54.49% (95% CI: 22.55, 73.26)) was higher than the aVE results obtained in the analysis of the primary endpoints.

Additionally, efficacy analysis by strain was carried out, although not all clinical isolates could provide cell culture results. Results by strain were consistent with the overall efficacy results for both type A viruses (H1N1 and H3N2) and for type B Victoria lineage. Efficacy against B/Yamagata could not be determined due to the very low cases (only 4 cases of B/Yamagata in the 5 seasons), which is consistent with the failure to detect B/Yamagata viruses since March 2020. In any case, confidence intervals were wide due to the smaller number of cases.

The minimum number of RT-PCR confirmed cases and of antigenically matched culture confirmed cases required for final efficacy analysis were obtained before the end of the fifth influenza season. Therefore, the analysis was carried out without the analysis of the totality of the samples that were finally collected. These extra cases and their analysis were provided for information only. This approach is endorsed.

Moreover, aVE analysis was also performed in different subgroups: age, vaccination history, race, sex, country and season. These analyses were not powered for hypothesis testing and therefore are descriptive results with wide confidence intervals in some cases. None of these analyses questioned the superior aVE of the QIVc vs the comparator.

Regarding the two age groups, a higher point estimate was observed in the older age subgroup compared with the younger age subgroup for both RT-PCR confirmed influenza due to any strain (47.24%, 95% CI: 26.62, 62.06 vs 32.77%, 95% CI: 3.22, 53.29) and culture confirmed influenza due to matched strains (54.29%, 95% CI: 24.20, 72.43 vs 36.60%, 95% CI: -8.56, 62.98). This result is consistent with previous results in other clinical studies carried out with this vaccine and is probably related to the weaker immune response in influenza naïve individuals, which are usually more abundant in the younger age group.

Of the 5691 subjects in the FAS Efficacy, only 110 subjects were previously vaccinated against influenza. In total, there were only 6 cases of RT-PCR confirmed influenza (any strain) and 4 cases of culture confirmed influenza in this subgroup, and no firm interpretation could be made.

In the subgroups by race, only robust results were obtained for some races. The Asian population was the most numerous, and had aVE point estimates consistent with the results obtained in the overall population.

In the same way, subgroup analysis by sex was also positive in both subpopulations and in line with the general aVE results.

The results obtained by country were very variable, nine (out of 15) countries had 14 or less RT-PCR confirmed influenza cases and no firm conclusions could be made. There were three countries in which a robust aVE analysis could be made, and the results are positive and similar as the other obtained point estimates.

Regarding the study seasons, the number and distribution of cases varied by season. Moreover, the surveillance in the NH 2020/2021 season yielded few influenza cases due to the pandemic declaration in March 2020. Robust point estimates of aVE for QIVc were observed in season 4 and 5 and were in line with the rest of the results.

In the efficacy analysis by season and strain (CSR – Table 14.2.1.1.13), it is noted that during seasons 1 and 2 (SH19 and NH19/20) there was apparently no efficacy for RT-PCR confirmed Influenza cases due to B strains: For season 1 there were 21 cases in QIVc group vs 22 in the Comparator group, while for season 2 there were 6 cases in each group. This was mostly due to an apparent lack of efficacy for B/Victoria strain: 17 cases in each group during Season 1, and 5 cases (QIVc) vs 3 cases (Comparator) during Season 2. During both seasons, the B/Victoria strain was the same. The MAH provided a reasonable explanation for the low immunogenicity and the apparent lack of efficacy of the vaccine against the Victoria strain in seasons 1 and 2 of the V130_14 study.

Overall the data and analysis are considered adequate.

Immunogenicity data

As explained by the MAH, the A/H3N2 strains for seasons 1 and 3 did not agglutinate red blood cells in the HI assay. This is due to due to recent evolutionary changes in the amino acids of the surface proteins hemagglutinin (HA) and neuraminidase (NA) of A/H3N2 viruses, resulting in a diminished capacity of HA to agglutinate target red blood cells in the HI assay. Thus, it is acceptable that for seasons 1 and 3, the Microneutralization assay is considered the primary immunogenicity assay.

Hemagglutination Inhibition Assay

Baseline HI GMT were variable across strain and season, but comparable in each of them between QIVc and the comparator vaccine groups.

Overall, QIVc was immunogenic across seasons eliciting highly variable HI responses with GMR in the range of 2.59-19.20 (A/H1N1), 1.81-7.43 (A/H3N2), 1.95-8.04 (B/Yamagata) and 1.43-32.55 (B/Victoria). Seroconversion rates were also variable, higher for A strains (A/H1N1: 29.89-75%; A/H3N2: 44.83-84.26%) than for B/strains (B/Yam: 23.42-66.67%; B/Vic: 9.91-80.56%).

For seasons 2 and 3, the results show low immunogenicity for B/Victoria strain: GMR were 1.79 and 1.43 (with 95% CI overlapping with the comparator vaccine), and seroconversion achieved only 13.08% and 9.91%, respectively.

Microneutralization Assay

Baseline MN GMT were variable across strain and season, but comparable in each of them between QIVc and the comparator vaccine groups.

Overall, QIVc elicited a neutralizing antibody response for the four strains across the 5 seasons, with the exception of B/Victoria strain during Season 2, when no rise in antibody titres was detected (GMR: 1.04) and there was no seroconversion (0.93%).

Other than season 2, the MN antibody response was highly variable across seasons, with GMR in the range of 2.37-17.55 (A/H1N1), 2.14-5.92 (A/H3N2), 1.82-3.93 (B/Yamagata) and 2.17-31.51 (B/Victoria). Seroconversion rates were also variable and in the range of 32.18-87.39% (A/H1N1), 20.56-71.30% (A/H3N2), 19.54-54.63% (B/Yamagata) and 20.54-94.44% (B/Victoria).

2.4.4. Conclusions on the clinical efficacy

The purpose of this submission is to support the use of cell-derived trivalent influenza vaccine (TIVc) for people aged 6 months and older based on additional data from the V130_14 study. TIVc was granted marketing authorization for use in people 2 years and older on 15 November 2024 based on evidence from the clinical development of TIVc and QIVc.

The data submitted in this application from study V130_14 have been generated with QIVc, but it is relevant to TIVc because both vaccines are manufactured using the same process and have overlapping compositions.

Both pre-specified success criteria for the primary endpoints 1a and 1b were met, so absolute vaccine efficacy (aVE) was demonstrated for QIVc versus the non-influenza comparator vaccine. The primary objective of efficacy was considered to be achieved if efficacy was demonstrated for at least one of the two primary efficacy endpoints. Both primary efficacy endpoints met the success criteria, therefore the primary objective of the study was achieved. For RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 41.26% (97.98% CI: 21.55, 56.02). For culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to vaccine strain the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 46.90% (97.5% CI: 19.19, 65.11).

Moreover, aVE analyses was also performed by stratifying according to the following subgroups: age, vaccination history, race, sex, country and season. None of these analyses questioned the superior aVE of the vaccine versus the comparator.

Additionally, the vaccine has been proven to be immunogenic across different seasons, both in terms of HI and MN antibodies; although there is uncertainty regarding the low immunogenicity observed for B/Victoria strain and its effect on clinical efficacy during seasons 1 and 2.

In conclusion, the data provided support the indication for prophylaxis of influenza in subjects of 6 months of age and older for the TIVc Flucelvax.

2.5. Clinical safety

Introduction

The key safety outcomes to support the use of cell-derived trivalent influenza vaccine (TIVc) for people aged 6 months and older based on additional data from the V130_14 study. TIVc was granted marketing authorization for use in people 2 years and older on 15 November 2024 based on evidence from the clinical development of TIVc and QIVc. In addition, TIVc was authorised for use in the US on 4 March 2024 for use in ages 6 months and older.

The data generated during development of QIVc is relevant to TIVc because both vaccines are manufactured using the same process and have overlapping compositions.

Table 14 Overview of Clinical Study V130_14

Study Number (Phase) Year Started	**Study Objectives**	**Study Design/Type of Control (number of centers)**	**Study Vaccines**	**Number of Subjects Exposed (M, F)**	**Subjects' Ages Geographic Location**

V130_14 (Phase 3) 2019	Efficacy Immunogenicity Safety	Randomized, comparator-controlled, observer-blind study (75)	QIVc NeisVac-C meningococcal group C polysaccharide conjugate vaccine	2856 (1440, 1416) 2841 (1518, 1323)	6 months through 47 months of age at enrollment Bangladesh, Bulgaria, Czech Republic, Estonia, Honduras, Latvia, Malaysia, New Zealand, Pakistan, Philippines, Poland, Romania, South Africa, Thailand, Ukraine

Source: Section 5.3.5.1, V130_14 CSR.

Abbreviations: F = female; M = male; QIVc = cell-based quadrivalent subunit influenza virus vaccine.

In Europe, QIVc is currently approved for Prophylaxis of influenza in adults and children from 2 years of age since October 2020. In the US, the FDA granted an extension to 6 months and older, approved in October 2021.

In addition, QIVc is authorised for use in adults and children from 6 months of age and older in Argentina (November 2021), Canada (March 2022), Taiwan (June 2022), Australia (July 2023), New Zealand (July 2023), and Great Britain (October 2023).

Patient exposure

A total of 5723 subjects 6 months through 47 months of age were enrolled in Study V130_14. In total, 5697 subjects received at least 1 dose of study vaccine (2857 subjects received QIVc and 2840 subjects received non-influenza vaccine comparator [NeisVac-C]). The majority of subjects (97.2%) completed the study.

Table 15 Study Disposition – As Randomized – All Enrolled Set, Study V130_14

	QIVc N=2860 n (%)	Comparator N=2863 n (%)	Total N=5723 n (%)
Total number of subjects enrolled	2860 (100)	2863 (100)	5723 (100)
Total number of subjects exposed	2857 (99.9)	2840 (99.2)	5697 (99.5)
Completed protocol	2794 (97.7)	2766 (96.6)	5560 (97.2)
Primary reason for discontinuation from the study	66 (2.3)	97 (3.4)	163 (2.8)
Adverse event	0	0	0
Death	1 (<0.1)	2 (0.1)	3 (0.1)
Withdrawal of consent	37 (1.3)	45 (1.6)	82 (1.4)
Lost to follow-up	19 (0.7)	25 (0.9)	44 (0.8)
Protocol deviation	0	2 (0.1)	2 (<0.1)
Study Terminated by Sponsor	0	0	0
Other	9 (0.3)	23 (0.8)	32 (0.6)

Source: Section 5.3.5.1, V130_14 CSR, Table 10-1.

Abbreviations: QIVc = cell-based quadrivalent subunit influenza virus vaccine.

Note 1: As randomized: according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received. One subject was randomized to the QIVc group, but received the comparator vaccine at Visit 1; this subject is included in the QIVc group "as randomized" and in the comparator vaccine group "as treated".

Demographic and Other Characteristics of Study Population

In Study V130_14, the QIVc and comparator vaccine groups in the All Enrolled Set were balanced with respect to demographic and baseline characteristics such as age, sex, race/ethnicity, and influenza vaccination history.

In FAS Efficacy, the mean age was 25.8 months and the range was 6 months to 47 months of age. As planned, at least 30% of subjects were 6 months through 23 months of age and at least 30% of subjects were 24 months through 47 months of age (44.2% and 55.8%, respectively).

The majority of subjects were White (43.2%) or Asian (38.3%).

Overall, only 1.9% of subjects were previously vaccinated against influenza (and thus scheduled to receive 1 dose of study vaccine) and 98.1% of subjects were not previously vaccinated against influenza (and thus scheduled to receive 2 doses of study vaccine).

At least 1 medical disorder was reported as medical history for 19.7% of subjects, with similar proportions in the 2 vaccine groups (QIVc: 20.0%; comparator vaccine: 19.5%). The most frequently reported medical history condition by System Organ Class (SOC) in both groups was Infections and Infestations (QIVc: 11.4%; comparator vaccine: 10.7%). The most frequently reported medical history conditions by Preferred Term (PT) were upper respiratory tract infection (QIVc: 2.3%; comparator vaccine: 2.0%) and rhinitis (QIVc: 1.5%; comparator vaccine: 1.4%).

Use of at least 1 concomitant medication was reported during the entire study period by 38.8%, with similar use of concomitant medications in the 2 vaccine groups (QIVc: 39.1%; comparator vaccine: 38.4%). The most frequently reported type of concomitant medication in both the QIVc and comparator vaccine groups was analgesics (QIVc: 23.6%; comparator vaccine: 22.7%).

In 2.7.4 Summary of clinical safety, the Demographics and Baseline Characteristics were not provided. The values described in this report have been summarized from 2.7.3 Summary Clinical efficacy. The demographic and baseline characteristics from the FAS Efficacy (99.4% of participants) were well balanced between the QIVc group and the comparator vaccine group and were consistent with those of the All Enrolled Set.

There were 44.2% aged 6 months to 23 months and 55.8% aged 24 months to 47 months. The distribution by sex were homogenous between groups (48.1% were female and 51.9% were male). The majority of subjects were White (43.2%) or Asian (38.3%) and were not previously vaccinated against influenza (98.1%). There were only 1.9% of subjects (48 participants in QIVc group and 62 participants in comparator group) who had been previously vaccinated against influenza.

Similar percentages of participants in both groups reported at least 1 medical disorder in both groups (20% in QIVc and 19.5% in comparator vaccine), mainly by SOC infection and Infestations and the use of at least 1 concomitant medication (39.1% in QIVc and 38.4% in comparator group), manly by analgesics.

Adverse events

In Study V130_14, Solicited AEs were collected at 30 minutes after vaccination by a qualified member of the study staff and recorded on source documents. The subject's parent/Legally Acceptable Representative (LAR) recorded solicited AEs on a Subject Diary Card from Day 1 through Day 7.

All unsolicited AEs were collected during the treatment period, which was from Day 1 to Day 29 for previously vaccinated subjects who received 1 dose of vaccine and from Day 1 to Day 57 for not previously vaccinated subjects who received 2 doses of vaccine.

During the follow-up period, from Day 30 or Day 58 (depending on previous influenza vaccination history) up to the study completion visit, only unsolicited AEs (and the medications used to treat them) that met the following criteria were collected: serious adverse events (SAEs), AEs leading to new onset of chronic disease (NOCD), AEs leading to withdrawal, and medically-attended AEs occurring within 30 days of influenza-like illness (ILI) onset.

Solicited Adverse Events

At 30 minutes after any vaccination, the percentages of subjects reporting any solicited AEs were similar between the QIVc (20.8%) and comparator vaccine (20.1%) groups.

In the 7-day period after any vaccination, the percentage of subjects reporting any solicited AE was 55.8% and 60.8% in the QIVc and comparator vaccine groups, respectively. The percentage of subjects reporting solicited local AEs was lower in the QIVc group than the comparator vaccine group (32.3% vs 40.4%); the percentage of subjects reporting solicited systemic AEs was similar between the 2 vaccine groups (40.9% vs 42.5%). The use of antipyretic/analgesics for treatment or prevention of pain/fever was similar between the QIVc and comparator vaccine groups (14.5% vs 15.0%).

In the QIVc group, the percentage of subjects reporting solicited local AEs was similar in the 7-day period after Vaccination 1 and Vaccination 2 (23.9% and 23.1%, respectively), while the percentage of subjects reporting solicited systemic AEs was higher after Vaccination 1 than Vaccination 2 (30.9% vs 23.6%, respectively). In the comparator vaccine group, the percentage of subjects reporting solicited AEs was higher after Vaccination 1 (MenC vaccine) than Vaccination 2 (saline for injection placebo) for both solicited local (36.6% vs 20.3%) and solicited systemic (32.9% vs 23.3%) AEs.

The percentages of subjects using analgesics/antipyretics in the 7-day period after any vaccination were similar between the QIVc and comparator vaccine groups for the prevention and treatment of pain and/or fever.

Solicited Local Adverse Events

The percentage and number of subjects who reported any solicited local adverse event were summarized in Table 16.

Table 16 Number (%) of Subjects 6 Months Through 47 Months of Age with Solicited Local Adverse Events from Day 1 Through Day 7 After Vaccination – As Treated – Solicited Safety Set, Study V130_14

	After Any Vaccination		After Vaccination 1		After Vaccination 2	
Solicited Local Adverse Event	**QIVc N=2813 n (%)**	**Comparator N=2790 n (%)**	**QIVc N=2810 n (%)**	**Comparator N=2787 n (%)**	**QIVc N=2752 n (%)**	**Comparator N=2712 n (%)**
Induration	**n=2812**	**n=2787**	**n=2790**	**n=2765**	**n=2745**	**n=2701**
Any	393 (14.0)	675 (24.2)	274 (9.8)	614 (22.2)	257 (9.4)	259 (9.6)
Severe	2 (0.1)	4 (0.1)	1 (<0.1)	4 (0.1)	1 (<0.1)	0
Erythema	**n=2813**	**n=2786**	**n=2786**	**n=2759**	**n=2745**	**n=2700**
Any	555 (19.7)	760 (27.3)	384 (13.8)	687 (24.9)	396 (14.4)	320 (11.9)
Severe	4 (0.1)	8 (0.3)	1 (<0.1)	7 (0.3)	3 (0.1)	1 (<0.1)
Ecchymosis	**n=2813**	**n=2786**	**n=2785**	**n=2757**	**n=2746**	**n=2700**
Any	261 (9.3)	294 (10.6)	177 (6.4)	240 (8.7)	170 (6.2)	143 (5.3)
Severe	4 (0.1)	3 (0.1)	4 (0.1)	1 (<0.1)	0	2 (0.1)
Tenderness	**n=2812**	**n=2790**	**n=2801**	**n=2777**	**n=2745**	**n=2710**
Any	628 (22.3)	716 (25.7)	412 (14.7)	595 (21.4)	422 (15.4)	339 (12.5)
Severe	29 (1.0)	34 (1.2)	13 (0.5)	24 (0.9)	19 (0.7)	13 (0.5)

Source: Section 5.3.5.1, V130_14 CSR, Table 12-4.

Abbreviations: QIVc = cell-based quadrivalent subunit influenza virus vaccine.

Note 1: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Note 2: For induration, ecchymosis, and erythema, severe was defined as >50 mm. For subjects <24 months of age at time of first dose of study vaccine, severe tenderness was defined as "cried when limb was moved/spontaneously painful"; for subjects ≥24 months of age at time of first dose of study vaccine, severe tenderness was defined as "prevents daily activity".

Note 3: Percentages are based on the number of events (n) in each vaccine group in the Solicited Safety Set.

The percentages of subjects reporting induration (14.0% vs 24.2%) and erythema (19.7% vs 27.3%) after any vaccination were lower in the QIVc group than the comparator vaccine group; the percentages of subjects reporting ecchymosis (9.3% vs 10.6%) and tenderness (22.3% vs 25.7%) were similar between the 2 vaccine groups. The most frequently reported solicited local AE was tenderness in the QIVc group (22.3% of subjects) and erythema in the comparator vaccine group (27.3% of subjects).

The majority of solicited local AEs after any vaccination were mild or moderate in severity in both the QIVc and comparator vaccine groups. The percentage of subjects reporting severe induration, erythema, or ecchymosis was <0.5% in both vaccine groups; the percentage of subjects reporting severe tenderness was 1.0% in the QIVc group and 1.2% in the comparator vaccine group.

In both the QIVc and comparator vaccine groups, the majority of subjects with induration, erythema, ecchymosis, or tenderness after any vaccination reported these events for ≤3 days.

In general, the percentages of subjects reporting individual solicited local AEs were similar after Vaccination 1 and Vaccination 2 in the QIVc group; for the comparator vaccine group, the percentage of subjects reporting solicited local AEs was higher after Vaccination 1 than Vaccination 2. This finding may be partly explained by Vaccination 1 being MenC vaccine and Vaccination 2 being saline for injection placebo.

Solicited Systemic Adverse Events

The percentage and number of subjects who reported any solicited systemic adverse event were summarized in Table 17.

Table 17 Number (%) of Subjects 6 Months Through 47 Months of Age with Solicited Systemic Adverse Events from Day 1 through Day 7 After Vaccination – As Treated – Solicited Safety Set, Study V130_14

	After Any Vaccination		After Vaccination 1		After Vaccination 2	
Solicited Systemic Adverse Event	**QIVc N=2813 n (%)**	**Comparator N=2790 n (%)**	**QIVc N=2810 n (%)**	**Comparator N=2787 n (%)**	**QIVc N=2752 n (%)**	**Comparator N=2712 n (%)**
Change of eating habits	**n=2813**	**n=2790**	**n=2808**	**n=2783**	**n=2747**	**n=2711**
Any	441 (15.7)	452 (16.2)	301 (10.7)	308 (11.1)	224 (8.2)	218 (8.0)
Severe	36 (1.3)	44 (1.6)	25 (0.9)	28 (1.0)	13 (0.5)	22 (0.8)
Sleepiness	**n=2813**	**n=2790**	**n=2808**	**n=2783**	**n=2747**	**n=2710**
Any	486 (17.3)	508 (18.2)	355 (12.6)	370 (13.3)	238 (8.7)	219 (8.1)
Severe	32 (1.1)	29 (1.0)	26 (0.9)	20 (0.7)	10 (0.4)	14 (0.5)
Vomiting/throwing up	**n=2813**	**n=2790**	**n=2808**	**n=2782**	**n=2747**	**n=2710**
Any	187 (6.6)	205 (7.3)	121 (4.3)	126 (4.5)	77 (2.8)	91 (3.4)
Severe	12 (0.4)	16 (0.6)	9 (0.3)	8 (0.3)	4 (0.1)	9 (0.3)
Diarrhea/loose stools	**n=2813**	**n=2787**	**n=2801**	**n=2779**	**n=2748**	**n=2707**
Any	371 (13.2)	371 (13.3)	265 (9.5)	262 (9.4)	163 (5.9)	183 (6.8)
Severe	31 (1.1)	31 (1.1)	22 (0.8)	18 (0.6)	10 (0.4)	14 (0.5)
Irritability	**n=2813**	**n=2790**	**n=2808**	**n=2784**	**n=2747**	**n=2710**
Any	595 (21.2)	643 (23.0)	442 (15.7)	482 (17.3)	324 (11.8)	318 (11.7)
Severe	41 (1.5)	43 (1.5)	34 (1.2)	31 (1.1)	9 (0.3)	16 (0.6)
Shivering	**n=2813**	**n=2790**	**n=2808**	**n=2783**	**n=2747**	**n=2710**
Any	111 (3.9)	113 (4.1)	68 (2.4)	72 (2.6)	52 (1.9)	49 (1.8)
Severe	2 (0.1)	6 (0.2)	1 (<0.1)	3 (0.1)	1 (<0.1)	3 (0.1)
Fever	**n=2813**	**n=2790**	**n=2810**	**n=2784**	**n=2750**	**n=2711**
Any (≥38.0°C)	306 (10.9)	305 (10.9)	172 (6.1)	167 (6.0)	158 (5.7)	156 (5.8)
Moderate (≥39.0°C to <40°C)	54 (1.9)	57 (2.0)	28 (1.0)	26 (0.9)	27 (1.0)	32 (1.2)
Severe (≥40.0°C)	3 (0.1)	4 (0.1)	3 (0.1)	2 (0.1)	0	2 (0.1)

Source: Section 5.3.5.1, V130_14, Table 12-5.

Abbreviations: QIVc = cell-based quadrivalent subunit influenza virus vaccine.

Note 1: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Note 2: Severe change of eating habits was defined as "missed more than 2 feeds/meals"; severe sleepiness was defined as "sleeps most of the time and it is hard to arouse him/her"; severe vomiting/throwing up was defined as "6 or more times in 24 hours or requires intravenous hydration"; severe diarrhoea/loose stools was defined as "6 or more loose stools in 24 hours or requires intravenous hydration"; severe irritability was defined as "unable to console"; severe shivering was defined as "prevents daily activity".

Note 3: Percentages are based on the number of events (n) in each vaccine group in the Solicited Safety Set.

The percentages of subjects reporting each specific solicited systemic AE after any vaccination were similar between the QIVc group and the comparator vaccine group (Table 17). The most frequently reported solicited systemic AE was irritability in both vaccine groups (QIVc: 21.2%; comparator vaccine: 23.0%).

The majority of solicited systemic AEs after any vaccination were assessed as mild or moderate in severity in both the QIVc and comparator vaccine groups. The percentage of subjects reporting a severe grading for an individual solicited systemic AE was <2.0% in both vaccine groups. The percentage of subjects reporting moderate fever (≥39.0ºC to <40°C) was low in both vaccine groups (QIVc: 1.9%; comparator vaccine: 2.0%), and the percentage of subjects reporting severe fever (≥40.0ºC) was 0.1% for both vaccine groups.

In both the QIVc and comparator vaccine groups, the majority of subjects reported an individual solicited systemic AE for ≤3 days.

No difference was observed regarding the frequency of solicited AE through 30 minutes after vaccination between QIVc and comparator group (20.8% and 20.1%, respectively).

The percentage of subjects reporting any solicited AE was 55.8% in QIVc group and 60.8% in comparator groups. The percentage of subjects reporting solicited local AEs was lower in the QIVc group than the comparator vaccine group (32.3% vs 40.4%); the percentage of subjects reporting solicited systemic AEs was similar between the 2 vaccine groups (40.9% vs 42.5%).

After Vaccination 1, in QIVc, the frequencies of solicited local and systemic AEs were 23.9% and 30.9%, compared to 36.6% and 32.6% in comparator group (Men C vaccine), respectively. These results show that QIVc was less reactogenic, mainly in local reactions, than MenC vaccine.

After Vaccination 2, in QIVc, the frequencies of solicited local and systemic AEs were 23.1% and 23.6%, compared to 20.3% and 23.3% in comparator group (Placebo), respectively. No difference between groups was observed after vaccination 2, showing that the second dose of QIVc had the same reactogenicity than the placebo.

In QIVc, the percentage of subjects reporting solicited local AEs was similar after Vaccination 1 and Vaccination 2 (23.9% and 23.1%, respectively), while the percentage of subjects reporting solicited systemic AEs was higher after Vaccination 1 than after Vaccination 2 (30.9% vs 23.6%, respectively).

In QIVc, the most frequently solicited local AEs were tenderness (22.3%) and erythema (19.7%), followed by induration (14%) and ecchymosis (9.3%). The incidence of each was similar after vaccination 1 and vaccination 2. In addition, comparing with comparator group, the incidence of each solicited local AEs after vaccination 1 was lower in QIVc group than in comparator group (Men C vaccine) and, as expected, the incidence after vaccination 2 was higher in QIVc than in comparator group (placebo).

The majority of solicited local AEs after any vaccination were mild or moderate in severity and were resolved in few days in both the QIVc and comparator vaccine groups. The incidence of each severe solicited AEs was <1% for all of them in both groups (the highest frequency in QIVc of severe solicited local AEs was tenderness after dose 2 [0.7%]).

In QIVc, the most frequently solicited systemic AEs were irritability (21.2%), sleepiness (17.3%) and change of eating habits (15.7%), followed by diarrhoea/loose stools (13.2%) and vomiting (6.6%). The incidence of each in QIVc was higher after vaccination 1 than vaccination 2. In addition, comparing with comparator group, the incidence of each solicited systemic AEs after vaccination 1 was similar or slightly lower in QIVc group than in comparator group (Men C vaccine) and, the incidence after vaccination 2 was similar between QIVc and comparator (placebo) groups.

The majority of solicited systemic AEs after any vaccination were mild or moderate in severity and were resolved in few days after vaccination in both vaccine groups. The incidence of each severe solicited systemic AEs in QIVc was <1%, except irritability (1.2%) after dose 1.

Fever (≥38º) was reported by 10.9% of participants in QIVc after any dose. Sever fever (≥40º) was reported by 0.1% (4 participants after dose 1 and 2 participants after dose 2).

In addition, the percentages of subjects using analgesics/antipyretics after any vaccination were similar between the QIVc and comparator vaccine groups for the prevention and treatment of pain and/or fever.

Unsolicited adverse Events

During the treatment period (Day 1 to Day 29/57), similar proportions of subjects reported any unsolicited AEs (42.5% and 45.4%, respectively) and medically-attended AEs (26.7% and 28.4%, respectively) in the QIVc and comparator vaccine groups.

All-causality unsolicited AEs reported by >1% of subjects in any group during the treatment period (from Day 1 through Day 29/57) are summarized by PT in Table 18, along with the associated related unsolicited AEs.

The most frequently reported unsolicited AEs were upper respiratory tract infection (QIVc: 346 subjects [12.1%]; comparator vaccine: 379 subjects [13.3%]) followed by rhinitis (QIVc: 228 subjects [8.0%]; comparator vaccine: 238 subjects [8.4%]) (Table 18). The majority of unsolicited AEs reported were mild or moderate in severity in both vaccine groups

The proportion of subjects assessed as having related unsolicited AEs was low overall and there was no notable difference between the QIVc and the comparator vaccine groups (Table 18).

Table 18 Number (%) of Subjects 6 Months Through 47 Months of Age with Any or Related Unsolicited Adverse Events After Any Vaccination with Onset From Day 1 Through Day 29/57a by Preferred Term (Occurring in >1% in Any Group) – As Treated – Unsolicited Safety Set, Study V130_14

	All Causality AEs		At Least Possibly Related AEs	
Preferred Term	**QIVc N=2856 n (%)**	**Comparator N=2841 n (%)**	**QIVc N=2856 n (%)**	**Comparator N=2841 n (%)**
Upper respiratory tract infection	346 (12.1)	379 (13.3)	21 (0.7)	16 (0.6)
Rhinitis	228 (8.0)	238 (8.4)	4 (0.1)	1 (<0.1)
Nasopharyngitis	126 (4.4)	113 (4.0)	4 (0.1)	4 (0.1)
Cough	86 (3.0)	107 (3.8)	5 (0.2)	5 (0.2)
Gastroenteritis	58 (2.0)	67 (2.4)	16 (0.6)	7 (0.2)
Diarrhoea	54 (1.9)	48 (1.7)	13 (0.5)	3 (0.1)
Pyrexia	49 (1.7)	46 (1.6)	7 (0.2)	3 (0.1)
Respiratory tract infection	47 (1.6)	48 (1.7)	1 (<0.1)	0
Influenza like illness	44 (1.5)	50 (1.8)	7 (0.2)	10 (0.4)
Viral infection	38 (1.3)	40 (1.4)	2 (0.1)	3 (0.1)
Pharyngitis	36 (1.3)	45 (1.6)	0	0
Rhinorrhoea	35 (1.2)	38 (1.3)	5 (0.2)	4 (0.1)
Bronchitis	33 (1.2)	57 (2.0)	1 (<0.1)	0
Respiratory tract infection viral	25 (0.9)	33 (1.2)	1 (<0.1)	2 (0.1)
Pneumonia	24 (0.8)	34 (1.2)	2 (0.1)	1 (<0.1)

Source: Section 5.3.5.1, V130_14 CSR, Table 12-7.

Abbreviations: QIVc = cell-based quadrivalent subunit influenza virus vaccine.
[a] Day 29 for previously vaccinated subjects (receiving a single dose of study vaccine) and Day 57 for not previously vaccinated subjects (receiving 2 doses of study vaccine).
Note 1: Related AEs include AEs that were considered to be at least possibly related to the study vaccine by the Investigator.

During the entire study period (Day 1 through Study Completion), 57.4% of subjects in the QIVc group and 60.0% of subjects in the comparator vaccine group reported at least 1 unsolicited AE; unsolicited AEs assessed as related were reported by 4.2% of subjects in the QIVc group and 3.7% of subjects in the comparator vaccine group. The percentages of subjects reporting medically-attended AEs within 30 days of ILI onset were 28.9% in the QIVc group and 32.6% in the comparator vaccine group.

Regarding unsolicited AEs, the incidence of reporting unsolicited AEs was similar between groups (42.5% in QIVc and 45.4% control group). There was only one unsolicited AE by PT reported with an incidence >10%, upper respiratory tract infection. The rest of them were reported <10% and with similar frequency in both groups.

The proportion of subjects with related unsolicited AEs was low and similar in both groups (0.7% in QIVc and 0.6% in control group). Overall, no notable difference between groups was observed. There was an imbalance in the frequency of Gastroenteritis (0.6% vs 0.2%, respectively) and Diarrhoea (0.5% vs 0.1%, respectively). Diarrhoea was proposed to be included in the section 4.8 of the SmPC, but not gastroenteritis. This is endorsed, because it is considered that diarrhoea can encompass both PT.

Serious adverse event/deaths/other significant events

Serious adverse events

In total, 184 SAEs were reported by 148 subjects: 64 subjects (2.2%) in the QIVc group and 84 subjects (3.0%) in the comparator vaccine group.

By SOC, the most frequently reported was Infections and Infestations in both groups (QIVc: 53 subjects [1.9%]; comparator vaccine: 71 subjects [2.5%]). And by PT, the most frequently reported SAEs were pneumonia (QIVc: 15 subjects [0.5%]; comparator vaccine: 24 subjects [0.8%]) and gastroenteritis (QIVc: 8 subjects [0.3%]; comparator vaccine: 12 subjects [0.4%]) in both vaccine groups.

One SAE of pneumonia of moderate severity in a subject receiving the comparator vaccine was considered to be related to the study vaccine by the Investigator solely due to the temporal association with the receipt of the second dose of study vaccine. This SAE was assessed as not related to the study vaccine by the Sponsor because the subject's clinical presentation and diagnostic findings were consistent with a diagnosis of community acquired pneumonia, and the response to treatment with antibiotics was supportive of a bacterial aetiology. No other SAEs were assessed to be related to the study vaccine during the entire study period.

Nine febrile convulsions were reported as an SAE (5 subjects in the QIVc group and 3 subjects in the comparator vaccine group). All these events of febrile convulsion were assessed as not related to the study vaccine by the Investigator and the Sponsor, with intercurrent disease reported as the alternative cause. Two SAEs of febrile convulsion (one each group) had a temporal association with study vaccine (within 7 days). However, both of which were attributed to concurrent infections by the Investigator (dental abscess for the subject in the QIVc group; upper respiratory tract infection for the subject in the comparator vaccine group).

Events of NOCD were reported in <1% of subjects in either vaccine group.

Deaths

3 deaths were reported during the study (QIVc: 1 subject; comparator vaccine: 2 subjects). None of which were assessed as related to the study vaccine. The details were below:

- One subject in the QIVc group, in the 6 months through 23 months age group, had an SAE of craniocerebral injury with a fatal outcome.
- One subject in the comparator vaccine group, in the 6 months through 23 months age group, had an SAE of severe gastroenteritis with a fatal outcome.
- One subject in the comparator vaccine group, in the 24 months through 47 months age group, had an SAE of ventricular dysfunction, followed by an SAE of cardio-respiratory arrest with a fatal outcome.

There was not imbalance regarding the incidence of SAEs between groups. In total, there were reported 184 SAEs in 148 subjects (64 subjects [2.2%] in the QIVc group and 84 subjects [3.0%] in the comparator vaccine group). None of the SAEs reported in the QIVc group were assessed as related to the study vaccine. One SAE in the comparator vaccine group, a report of community acquired pneumonia was assessed as possibly related to the study vaccine by the Investigator and assessed as not related by the Sponsor.

There were 3 deaths (1 in QIVc group and 2 in comparator group). None of them were assessed as related.

Safety in special populations

Data from Study V130_14 in reference to standard intrinsic factors such as age, gender, and race indicate that there are no meaningful differences in the frequency of solicited or unsolicited AEs in these populations

Incidence of Adverse Events by Age

As observed for the overall study population, the percentage of subjects reporting solicited local AEs after any vaccination was lower in the QIVc group than the comparator vaccine group for both the 6 months through 23 months (31.8% vs 43.3%) and the 24 months through 47 months (32.6% vs 38.2%) age subgroups. The percentage of subjects reporting solicited systemic AEs after any vaccination was similar between the QIVc and comparator vaccine groups for both the 6 months through 23 months (45.1% vs 49.0%) and 24 months through 47 months (37.5% vs 37.3%) age subgroups.

In the QIVc group, the percentage of subjects reporting any solicited local AEs was similar in the 6 months through 23 months and 24 months through 47 months age subgroups; in the comparator vaccine group, the percentage of subjects reporting any solicited local AEs was higher in the younger age subgroup than the older age subgroup. In both vaccine groups, the percentage of subjects reporting any solicited systemic AEs was higher in the younger age subgroup than the older age subgroup. In the QIVc group, the percentages of subjects reporting irritability, sleepiness, and loose stools/diarrhoea were higher in the 6 months through 23 months age subgroup compared with the 24 months through 47 months age subgroup, while the percentages of subjects reporting change of eating habits, vomiting/throwing up, and shivering were similar between the 2 age subgroups. In the comparator vaccine group, the percentage of subjects reporting individual solicited systemic AEs were higher in the younger age subgroup than the older age subgroup apart from shivering. There were no notable differences in the rates of fever between the 2 age subgroups in the QIVc or comparator vaccine groups.

No notable differences in the percentages of subjects reporting any unsolicited AEs were observed between the QIVc and comparator vaccine groups in either the 6 months through 23 months age subgroup (59.6% vs 62.3%) or the 24 months through 47 months age subgroup (55.6% vs 58.2%). In the 6 months through 23 months age subgroup, the percentages of subjects reporting related unsolicited AEs were 4.3% and 4.5%, respectively, in the QIVc and comparator vaccine groups, and the percentages of subjects reporting

SAEs were 2.7% and 4.2%, respectively. In the 24 months through 47 months age subgroup, the percentages of subjects reporting related unsolicited AEs were 4.2% and 3.0%, respectively, in the QIVc and comparator vaccine groups, and the percentages of subjects reporting SAEs were 1.9% and 2.0%, respectively.

In both vaccine groups, the percentages of subjects reporting any unsolicited AEs or related unsolicited AEs were not notably different between the 2 age subgroups. In both vaccine groups, the percentage of subjects reporting SAEs was higher in the 6 months through 23 months age subgroup compared with the 24 months through 47 months age subgroup, although the percentages overall were low for both age subgroups.

As in the overall population, in the two age subgroups, the incidence of solicited local AEs was lower in QIVc than in the control group and the incidence of solicited systemic AEs or unsolicited AEs was similar between QIVc and the control group.

When comparing the two age subgroups, no difference was observed in the incidence of solicited local AEs or unsolicited AEs in QIVc. However, a higher frequency of solicited systemic AEs was observed in the younger age than in the older subgroup, mainly due to irritability, sleepiness, and loose stools/diarrhoea.

In addition, the percentage of subjects reporting SAEs was higher in the 6 months through 23 months of age subgroup compared with the 24 months through 47 months age subgroup. Considering that the most frequently reported SAE was by SOC "infection and infestations" and none of these SAE was assessed as related to the vaccine, it is expected that the incidence would be higher in the younger subgroup age due to their own age-related vulnerability. Therefore, this is not a safety concern.

Incidence of Adverse Events by Gender

As observed for the overall study population, the percentage of subjects reporting solicited local AEs after any vaccination was lower in the QIVc group than the comparator vaccine group for both the male and female subgroups. The percentage of subjects reporting solicited systemic AEs after any vaccination was similar between the QIVc and comparator vaccine groups for both the male and female subgroups.

In both vaccine groups, the percentages of subjects reporting solicited local and solicited systemic AEs were similar between the male and female subgroups.

No notable differences in the percentages of subjects reporting any unsolicited AEs, any related unsolicited AEs, or SAEs were observed between the QIVc and comparator vaccine groups in either the male or female subgroups.

In both vaccine groups, the percentages of subjects reporting any unsolicited AEs, any related unsolicited AEs, or SAEs were not notably different between the male and female subgroups.

Incidence of Adverse Events by Race

The percentage of subjects reporting solicited local AEs after any vaccination was lower in the QIVc group than the comparator vaccine group for the Black or African American (25.5% vs 34.9%) and White (52.4% vs 65.7%) subgroups; the percentage of subjects reporting solicited local AEs was similar between the 2 vaccine groups for the Asian (11.4% vs 14.3%) and Other (31.0% vs 32.4%) subgroups. The percentage of subjects reporting solicited systemic AEs after any vaccination was similar between the QIVc and comparator vaccine groups for each of the race subgroups (Black or African American: 49.0% vs 45.7%; White: 47.0% vs 50.0%; Asian: 30.7% vs 32.6%; Other: 43.9% vs 42.0%).

In both vaccine groups, the percentage of subjects reporting solicited local and solicited systemic AEs varied by race.

No notable differences in the percentages of subjects reporting any unsolicited AEs, related unsolicited AEs, or SAEs were observed between the QIVc and comparator vaccine groups within each race category.

Because of the small number of subjects in some of the race subgroups, the conclusions that can be drawn from comparisons between the race subgroups are limited.

As observed with other vaccines, the reactogenicity (solicited local and systemic AEs) was lower in Asian participants than in White participants. The Black or African American participants showed a lower incidence in solicited local AEs than in the white population, but a similar incidence of solicited systemic AEs. However, considering the small number of Black or African American subjects, no conclusions can be drawn.

In addition, no notable differences in the percentages of subjects reporting any unsolicited AEs, related unsolicited AEs, or SAEs were observed between the QIVc and comparator vaccine groups within each race category.

Incidence of Adverse Events by Influenza Vaccination History

Because of the small number of subjects in the previously vaccinated subgroup (n=110), the conclusions that can be drawn from comparisons between the 2 subgroups are limited.

As observed for the overall study population, the percentage of subjects reporting solicited local AEs after any vaccination was lower in the QIVc group than the comparator vaccine group for both previously vaccinated subjects and not previously vaccinated subjects. The percentage of subjects reporting solicited systemic AEs after any vaccination was lower in the QIVc group than the comparator vaccine group for previously vaccinated subjects and similar between the 2 vaccine groups for not previously vaccinated subjects.

In both vaccine groups, solicited local AEs were more frequently reported by previously vaccinated compared with no previously vaccinated subjects. In QIVc group, the percentage of subjects reporting solicited systemic AEs was higher in not previously vaccinated subjects (41.1%) than in vaccinated subjects (27,1%), while similar percentage were reported for not previously vaccinated subjects (42,6%) and previously vaccinated subjects (37.1%) in comparator vaccine.

No notable differences in the percentages of subjects reporting any unsolicited AEs were observed between the QIVc and comparator vaccine groups in previously vaccinated subjects and not previously vaccinated subjects.

Safety analysis by previous influenza vaccination status cannot be drawn because of the small number of subjects previously vaccinated. The limited data regarding solicited and unsolicited AEs in the previously vaccinated group seem to be similar than in the not previously vaccinated, and do not show any safety concern.

Incidence of Adverse Events by Country

Because of the small number of subjects enrolled in some of the countries, the conclusions that can be drawn from comparisons between country subgroups are limited.

There was considerable variability between the countries in the number of enrolled subjects and in the percentage of subjects reporting solicited local and solicited systemics AEs in the 7 day period after any vaccination. For countries that enrolled 200 subjects or more, the percentage of subjects in each country reporting solicited local AEs in the QIVc group was similar to or lower than that in the comparator vaccine group; the percentage of subjects reporting solicited systemic AEs was similar between the 2 vaccine groups.

In general, no notable differences in the percentages of subjects reporting any unsolicited AEs were observed between the QIVc and comparator vaccine groups within each country.

There was considerable variability between the countries in the number of enrolled subjects. For countries that enrolled 200 subjects or more (Estonia [n=625], Pakistan [n=249], Filipinas [n=605], Poland [n=211],

South Africa [n=373] and Ukraine [n=183]), as in the overall population, the incidence of solicited local AEs in participants who received QIVc was lower than in comparator groups, and the incidence of solicited systemic AEs was similar between groups.

In QIVc, regarding solicited local AEs, Estonia presented the highest incidence (50.4%), and Pakistan and Philippines the lowest (8.8% and 8.1%, respectively). Regarding solicited Systemic AEs, South Africa showed the highest incidence (48.8%) and Pakistan the lowest (17.3%).

Nevertheless, due to the variability of the enrolled subjects by country, it is not possible to draw any conclusion regarding these data.

Incidence of Adverse Events by Season/Year

The percentage of subjects reporting solicited local AEs after any vaccination in the QIVc group was similar to or lower than the percentage in the comparator vaccine group within each of the 5 influenza seasons of the study. The percentage of subjects reporting solicited systemic AEs after any vaccination was similar between the QIVc and comparator vaccine groups within each of the 5 influenza seasons.

In both vaccine groups, the percentage of subjects reporting solicited local and solicited systemic AEs varied between the 5 influenza seasons, which may reflect differences in the countries that participated in each season.

No notable differences in the percentages of subjects reporting any unsolicited AEs, related unsolicited AEs, or SAEs were observed between the QIVc and comparator vaccine groups within each influenza season.

The percentage of subjects reporting solicited local and solicited systemic AEs varied between the 5 influenza seasons. Overall, a higher incidence of solicited local and systemic AEs was reported in NH influenza seasons than in SH influenza seasons. The MAH indicated that this difference could reflect differences in the countries that participated in each season. This is endorsed and it is considered that the difference in race could also contribute to this observation.

No safety concern has been raised, as the reactogenicity profile per influenza season is considered acceptable.

Discontinuation due to adverse events

There were no subjects with AEs leading to study withdrawal. Three subjects in the comparator vaccine group had an AE leading to withdrawal from receipt of the second dose of the study vaccine.

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 post-marketing 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. With the WHO recommendation in 2023 to transition from quadrivalent to trivalent influenza vaccines for seasonal use, TIVc was recently approved in the EU on 15 Nov 2024 for use in adults and children 2 years of age and older. Marketing authorisation in the US was granted on 04 March 2024 for use in adults and children 6 months of age and older. 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. QIVc is currently approved for use in adults and children 6 months of age and older in the US and several other countries. 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), post-marketing experience with QIVc has not identified any safety concerns. No new safety concerns for QIVc have been identified through safety monitoring in clinical trials and in the post-marketing setting for children 6 months to 4 years of age. The marketing experience for both TIVc and QIVc to date is consistent with the favourable safety and tolerability profile demonstrated in the clinical development program for TIVc and QIVc.

2.5.1. Discussion on clinical safety

Within this procedure, the MAH provided the safety analysis of the completed Study V130_14 in children 6 months through 47 months of age.

There were 5697 subjects who received at least 1 dose of study vaccine. Of these, 2857 subjects received QIVc and 2840 subjects received non-influenza vaccine comparator [NeisVac-C].

The demographic and baseline characteristics were well balanced between the QIVc group and the comparator vaccine group. There were 44.2% aged 6 months to 23 months and 55.8% aged 24 months to 47 months. The distribution by sex was homogenous between groups (48.1% were female and 51.9% were male). The majority of subjects were White (43.2%) or Asian (38.3%) and had not been previously vaccinated against influenza (98.1%). Only 1.9% of subjects (48 participants in QIVc group and 62 participants in comparator group) had been previously vaccinated against influenza.

Similar percentages of participants in both groups reported at least 1 medical disorder in both groups (20% in QIVc and 19.5% in comparator vaccine), mainly by SOC infection and Infestations, and similar percentages of participants in both groups reported the use of at least 1 concomitant medication (39.1% in QIVc and 38.4% in comparator group), mainly analgesics.

Solicited Adverse Events

In Study V130_14, Solicited AEs were collected at 30 minutes after vaccination and on a Subject Diary Card from Day 1 through Day 7.

No difference was observed regarding the frequency of solicited AE through 30 minutes after vaccination between QIVc and comparator group (20.8% and 20.1%, respectively).

The percentage of subjects reporting any solicited AE (from Day 1 through Day 7) was 55.8% in QIVc group and 60.8% in comparator groups. The percentage of subjects reporting solicited local AEs was lower in the QIVc group than in the comparator vaccine group (32.3% vs 40.4%); the percentage of subjects reporting solicited systemic AEs was similar between the 2 vaccine groups (40.9% vs 42.5%).

After Vaccination 1, in QIVc, the frequencies of solicited local and systemic AEs were 23.9% and 30.9%, compared to 36.6% and 32.6% in comparator group (Men C vaccine), respectively. These results show that QIVc is less reactogenic than MenC vaccine, mainly regarding the local reactions.

After Vaccination 2, in QIVc, the frequencies of solicited local and systemic AEs were 23.1% and 23.6%, compared to 20.3% and 23.3% in comparator group (Placebo), respectively. No difference between groups was observed after vaccination 2, showing that second dose of QIVc had a similar reactogenicity than the placebo.

In QIV, the percentage of subjects reporting solicited local AEs was similar after Vaccination 1 and Vaccination 2 (23.9% and 23.1%, respectively), while the percentage of subjects reporting solicited systemic AEs was higher after Vaccination 1 than after Vaccination 2 (30.9% vs 23.6%, respectively).

In QIVc, the most frequently solicited local AEs were tenderness (22.3%) and erythema (19.7%), followed by induration (14%) and ecchymosis (9.3%). The incidence of each solicited local AE was similar after vaccination 1 and vaccination 2. In addition, comparing with comparator group, the incidence of each solicited local AEs after vaccination 1 were lower in QIVc group than in comparator group (Men C vaccine) and, as expected, the incidence after vaccination 2 was higher in QIVc than in the comparator group (placebo).

The majority of solicited local AEs after any vaccination were mild or moderate in severity and were resolved in few days in both, QIVc and comparator vaccine, groups. The incidence of each severe solicited AEs was <1% for all of them in both groups (the highest frequency in QIVc of sever solicited local AEs was tenderness after dose 2 [0.7%]).

In QIVc, the most frequently solicited systemic AEs were irritability (21.2%), sleepiness (17.3%) and change of eating habits (15.7%), followed by diarrhoea/loose stools (13.2%) and vomiting (6.6%). The incidence of each solicited systemic AE in QIVc was higher after vaccination 1 than after vaccination 2.

In addition, the incidence of each solicited systemic AE after vaccination 1 was similar or slightly lower in QIVc group than in the comparator group (Men C vaccine) and similar after vaccination 2, when comparing the incidences of solicited systemic AEs between QIVc and the placebo group.

The majority of solicited systemic AEs after any vaccination were mild or moderate in severity and were resolved in few days in both vaccine groups. The incidence of each severe solicited systemic AEs in QIVc was <1%, except for irritability (1.2%) after dose 1.

Fever (≥38º) was reported by 10.9% of participants in QIVc after any dose. Severe fever (≥40º) was reported by 0.1% (4 participants after dose 1 and 2 participants after dose 2).

In addition, the percentages of subjects using analgesics/antipyretics after any vaccination were similar between the QIVc and comparator vaccine groups for the prevention and treatment of pain and/or fever.

Unsolicited AEs

The incidence of reporting unsolicited AEs was similar between groups (42.5% in QIVc and 45.4% control group). There was only one unsolicited AE by PT reported with an incidence >10%, upper respiratory tract infection. The rest of them were reported <10% and with similar frequency in both groups.

The proportion of subjects with related unsolicited AEs was low and similar in both groups (4.2 % in QIVc and 3.7 % in control group). Overall, no notable difference between groups was observed, with the exception of gastroenteritis (0.6% vs 0.2%, respectively) and diarrhoea (0.5% vs 0.1%, respectively) where an imbalance was observed. Diarrhoea was proposed to be included in the section 4.8 of the SmPC by the MAH, but not gastroenteritis. This is endorsed, as it can be considered that diarrhoea can encompass both PT.

Deaths and SAE

There were 3 deaths (1 in QIVc group and 2 in comparator group). None of them were assessed has related.

There was not imbalance regarding the incidence of SAEs between groups. In total, there were reported 184 SAEs in 148 subjects (64 subjects [2.2%] in the QIVc group and 84 subjects [3.0%] in the comparator vaccine group). None of the SAEs reported in the QIVc group were assessed as related to the study vaccine. One SAE in the comparator vaccine group, a report of community acquired pneumonia, was assessed as possibly related to the study vaccine by the Investigator and assessed as not related by the Sponsor.

Subgroups analysis

There was a safety analysis by age, gender, race, country, Influenza Vaccination History and by Season/year. No analysis by extrinsic factors was done.

As in the overall population, in each subgroup analysis, the incidence of solicited local AEs was lower in QIVc than in control groups and the incidence of solicited systemic AEs or unsolicited AEs were similar between QIVc and control group.

However, in QIVc some difference regarding the reactogenicity profile was observed in some subgroups:

- No difference was observed in the incidence of solicited local AEs or unsolicited AEs by age. However, a higher frequency of solicited systemic AEs was observed in 6 to 23 months of age than in 24 to 47 months on age, mainly due to irritability, sleepiness, and loose stools/diarrhoea.
- No difference in the frequency of solicited or unsolicited AEs was observed by gender.
- Solicited local and systemic AEs were lower in Asian participants than in White participants. Considering the small number of Black or African American participants no conclusion can be drawn.
- Any safety analysis by previous influenza vaccination status cannot be drawn because of the small number of subjects previously vaccinated
- Due to the variability in the number of enrolled subjects by countries it is not possible to draw any conclusion.
- The percentage of subjects reporting solicited local and solicited systemic AEs varied between the 5 influenza seasons. Overall, a higher incidence of solicited local and systemic AEs was reported in NH influenza seasons than in the SH influenza seasons.

Overall, no difference was observed in the incidence of SAEs by subgroups, with the exception of age. The percentage of subjects reporting SAEs was higher in the 6 months through 23 months of age subgroup compared with the 24 months through 47 months age subgroup. Considering that the most frequently reported SAE were by SOC "infection and infestations" and none of these SAE were assed as related to the vaccine, it is expected that the incidence would be higher in the younger subgroup age due to their own age-related vulnerability.

Post marketing experience

The most recent PSUR (covering the period 16 March 2023 to 15 March 2024) covers the use of QIVc in the cohort age under evaluation (6 months through 47 months of age), because this age extension was approved in October 2021 by US FDA and in Argentina (November 2021), Canada (March 2022), Taiwan (June 2022), Australia (July 2023), New Zealand (July 2023), and Great Britain (October 2023) and did not rise any safety concern.

In addition, this PSUR and the post-marketing experience with QIVc has not identified any safety concerns

In conclusion**,** after assessing the submitted safety data collected in the phase III study V130_14, QIVc vaccine is well tolerated and has a good reactogenicity profile in subjects aged 6 months through 47 months of age, which is similar to the known pattern in older subjects. The majority of the AEs were mild or moderate in severity and were resolved in few days after vaccination.

The safety data and post-marketing experience do not raise any clinically relevant safety issue.

Therefore, the safety profile of QIVc is considered to be adequate to support the indication for Flucelvax TIVc for prophylaxis of influenza in subjects of 6 months and older. TIVc was authorised for use in ages 6

months and older in the US on 4 March 2024 and the post marketing experience with TIVc and QIVc indicated that no new safety concerns were identified.

2.5.2. Conclusions on clinical safety

The safety assessment of the EoI of Flucelvax (TIVc) to individuals aged 6 months and older is based mainly in on the data from the V130_14 study (also submitted for the extension of indication for Flucelvax Tetra (QIVc) (procedure number EMEA/H/C/004814/II/0047).

The assessment of the safety data of EoI from QIVc to support EoI to TIVc is in line with the safety assessment for the MA of Flucelvax (TIVc), that was derived from the data generated during development of Flucelvax tetra (QIVc); specifically during the MAA procedure (EMEA/H/C/004814) and during the variation for the EoI from 2 years of age (number procedure EMEA/H/C/004814/II/0013).

In summary, the data show that QIVc vaccine is well tolerated and has a good reactogenicity profile in subjects aged 6 months through 47 months of age. The majority of the AEs were mild or moderate in severity and were resolved in few days after vaccination. In addition, a higher frequency of solicited systemic AEs was observed in subjects 6 to 23 months of age than in those 24 to 47 months of age, mainly due to irritability, sleepiness, and loose stools/diarrhoea.

As is known, in subjects aged 2 years and older, the TIVc safety profile is in general comparable to that of QIVc. Therefore, TIVc would be expected to be well tolerated in subjects from 6 to 23 months of age and to have a similar safety profile than QIVc in this cohort.

Moreover, TIVc was authorised for use in ages 6 months and older in the US on 4 March 2024 and the post marketing experience with TIVc and QIVc indicated that no new safety concerns were identified.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted with this application an updated RMP with proposed amendments mainly reflecting the inclusion of indication and posology in children 6 months of age based on the results of the V130_14 clinical study in the paediatric population (6 to 47 months of age). The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.0 with the following content:

Safety concerns

Removal of safety concerns (Missing information):
Removal of "Safety in immunocompromised patients" and "Safety in subjects with underlying disease" as missing information from the list of safety concerns. Safety in immunocompromised patients and safety in subjects with underlying diseases, previously classified as missing information, have been removed from the list of safety concerns in EU RMP v4.0. At the DLP of this RMP, there are no missing information for TIVc and QIVc.

Table 19 ***SVIII.1 Summary of the safety concerns***

Summary of the safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine PV activities for Seqirus products comply with Good Pharmacovigilance Practices (GVP) and fulfil the legal requirements per Directive 2001/83/EC and Regulation (EC) No. 726/2004.

Other forms of routine pharmacovigilance activities for adverse events following immunisation:

The "Interim guidance on Enhanced Safety Surveillance for seasonal influenza vaccines in the EU" (EMA/PRAC/222346/2014) requires the implementation of annual Enhanced Safety Surveillance for influenza vaccines. It should be noted, however, that at the DLP of this RMP this interim guidance is under review by the EMA (Health Threats and Vaccines strategy (AF-HTV, 2023). In addition, at the Pharmacovigilance Risk Assessment Committee (PRAC) plenary meeting in April 2024, it was agreed to waive the requirement to submit enhanced safety surveillance data for all seasonal influenza vaccines (both national and centrally approved) while the 'Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU' (EMA/PRAC/222346/2014) is under review (PRAC, 2024). Seqirus still implemented the Enhanced Passive Safety Surveillance (EPSS) for QIVc during the NH 2024/2025 influenza season. In subsequent NH influenza seasons, implementation of EPSS for QIVc or TIVc in the EU will depend on the applicable guidance and any waivers in place at the time.

The passive approach of the Enhanced Safety Surveillance is classified as a routine PV activity and in accordance with chapter "V.B.6.1.2 RMP part III section Routine PV activities of the GVP Module V". A full description of the methodology, including the specific mechanisms to raise awareness with and facilitate spontaneous reports of adverse events for vaccine recipients, estimate near real-time vaccine exposure and its implementation is described in the EPSS Plan for each NH influenza season.

ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Required additional pharmacovigilance activities:

There are no additional PV activities required for TIVc or QIVc by the EMA.

Additional pharmacovigilance activities recommended under EMA guidelines:

To comply with the Guideline on Influenza vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014) of July 2016, a supporting Innovative Medicines Initiative (IMI) programme called on Development of Robust Innovative Vaccine Effectiveness (DRIVE) has been launched in July 2017. GSK, Sanofi Pasteur, Abbott and Seqirus, as vaccine manufacturers with marketed influenza vaccines in Europe, contributed to the genesis of the project. This project is a unique public-private partnership involving in addition to manufacturers, 11 partners including academic and public health institutes. DRIVE aims to assess the feasibility of building a sustainable platform in Europe able to generate brand specific influenza vaccine effectiveness data in Europe. As per the IMI legal framework, this is a 5-year partnership project, encompassing four consecutive influenza seasons. Studies are intended to be

conducted annually in European sites and the data generated will be pooled across participating centres, with the first pilot seasonal studies initiated during the NH 2017/2018 influenza season. Each year a report will be generated to synthesize data on influenza vaccine effectiveness collected across participating sites including data generated from the public health surveillances contributing to DRIVE. Results will be provided every year but will not trigger an RMP update unless the results impact public health or alter the benefit-risk profile of Seqirus vaccines, as per EMA agreement on 30 Apr 2019 (EMA/248552/2019 Vaccine Working Party). Seqirus will not be the study sponsor or owner of the data, and will not control the scientific deliverables, which include the Study Protocol, Statistical Analysis Plan and Study Reports. Timelines are driven by the overall project and conditioned notably by logistics associated with existing surveillances. Over its lifetime, the project is expected to progressively expand the existing infrastructure to enhance the opportunities for Seqirus to document vaccine effectiveness of its marketed influenza vaccines in Europe. It should be noted that the EMA granted a deferral on the requirement to provide brand-specific influenza vaccine effectiveness data for the 2022–2023, 2023-2024 and 2024-2025 NH seasons, and therefore no data from DRIVE has or will be generated for these seasons.

Table 20 Summary table of additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
None				
Additional pharmacovigilance activities recommended under EMA guidelines				
A non-interventional study of vaccine effectiveness; TIVc/QIVc versus no vaccination (DRIVE sub-analysis)	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 Q42020 and annually thereafter

Overall conclusions on the Pharmacovigilance Plan

The proposed post-authorisation Pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 21 Part V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern and population

Safety concern	Risk minimisation measures	Pharmacovigilance (PV) activities
Important identified risks:		
None		
Important potential risks:		
None		
Missing information:		

Safety concern	Risk minimisation measures	Pharmacovigilance (PV) activities
None		

2.7. Update of the Product information

As a consequence of this variation, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes are also made to the PI to bring it in line with the assessment of the initial MAA of Flucelvax as some changes were pending to be implemented (sections 4.4 and 4.5 of the SmPC).

Section 4.5 of the SmPC has been updated to comply with the MAH commitment at the time of the initial Marketing Authorisation to update this section to align it with the current QRD guideline.

Section 4.5 of Flucelvax already states that "Based on clinical experience Flucelvax can be given at the same time as other vaccines", as does the same section in the SmPC of Flucelvax Tetra. The clinical data that support this statement come from a clinical study conducted with Flucelvax.

During this procedure, the MAH presented a justification to maintain this statement without the need to submit any additional clinical data and the CHMP considers that this justification is acceptable. It is general practice and also in line with WHO guidance to co-administer seasonal inactivated influenza vaccines together with COVID-19 vaccines and/or pneumococcal vaccines. There is extensive experience on co-administration of inactivated seasonal influenza vaccines with other vaccines, and no safety signal has been raised as can be seen in the PSUR of Flucelvax Tetra.

In addition to the already existing statement (mentioned above), the MAH proposed the following text which is aligned with other company EU PI.

"If Flucelvax is to be used at the same time as another vaccine, it should be administered at separate injection sites and preferably on different limbs. It should be noted that the adverse reactions may be intensified by any co-administration." This additional text agreed.

The MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

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

The MAH 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 authorisation application (MAA) which was approved on 12 Dec 2018 (with the age indication from 9 years and older). As noted in the Europe Public Assessment Report (EPAR) from the original marketing authorisation, 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. The completed user testing with Flucelvax Tetra was considered applicable to Flucelvax (trivalent formulation) and supported the company assessment that no additional user testing was needed for the recently approved Flucelvax MAA (EMEA/H/C/006532/0000). With the current type II variation, the company is proposing to extend the Flucelvax indication in the paediatric population from 2+ years of age to 6+ months of age and older, based on the efficacy and safety results from clinical Study V130_14. The resulting changes to the Flucelvax Package Leaflet are considered very

minor and limited to minor changes in the frequencies of a few non-serious solicited adverse reactions. As such, given the approved population is only being lower by 1.5 years (from 2+ years to 6+ months), and there are no substantive changes to safety data or key safety messaging that would impact readability, no additional user testing is required to support the changes proposed in this procedure.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Influenza is a highly contagious infectious disease of global importance, with seasonal epidemics occurring predominantly during the winter months in the Northern and Southern Hemispheres. Annual vaccination is currently the most effective way to prevent influenza. Children <5 years of age, and particularly those <2 years of age, are at high risk of infection and of developing severe influenza and serious influenza-related complications (Izurieta et al. 2000; Bourgeois et al. 2006). An estimated 109.5 million influenza virus episodes were reported globally in 2018 in children <5 years of age, accompanied by an estimated 870,000 influenza-associated hospital admissions and 34,800 influenza-associated deaths (Wang et al. 2020). Young children are therefore a priority group for annual seasonal influenza vaccination throughout the world (WHO 2012; AAP 2016). Vaccination of children against influenza may also reduce community viral transmission (Mertz et al. 2016).

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 were trivalent influenza vaccines (TIVs) composed of antigens from 3 influenza strains: 2 influenza A strains (A/H1N1 and A/H3N2) and 1 influenza B strain (either B/Yamagata or B/Victoria). The inclusion of only 1 B strain in TIVs has resulted in a risk of mismatch between the vaccine and the circulating influenza B strain (Peltola, Ziegler, and Ruuskanen 2003; Hu et al. 2004). Avoiding this risk of mismatch has been especially important in children as influenza B infections are reported to occur more often in children than in adults and are associated with a higher risk of complications and mortality in children (Belshe 2010; Ambrose and Levin 2012). Quadrivalent influenza vaccines (QIVs) containing B strains from both lineages were therefore developed to give broader protection against circulating influenza viruses.

Flucelvax Tetra is a cell-based quadrivalent inactivated subunit influenza vaccine (QIVc) prepared from virus propagated in MDCK cells. The development of a cell culture-based manufacturing platform offers several advantages over conventional egg-based manufacturing platforms. In addition to an improved production process and a more rapid surge capacity in the event of a pandemic, the replication of influenza viruses in a cell-based system reduces the risk of egg-adaptive mutations in the virus hemagglutinin (HA) protein, leading to vaccine strains that are more closely matched to circulating wild-type influenza strains

(Lambert and Fauci 2010; Barr et al. 2018; Harding and Heaton 2018). Since the 2019-2020 influenza season, Flucelvax Tetra has been manufactured with cell-based candidate vaccine viruses for all 4 strains.

After the COVID-19 pandemic, the B/Yamagata influenza virus strain was confirmed to no longer be in circulation, and thus in September 2023, the WHO recommended a transition from quadrivalent influenza vaccines to trivalent influenza vaccines for seasonal influenza prophylaxis.

Subsequently, EMA/ETF recommended to exclude B/Yamagata from the live attenuated vaccine since 2024/2025, and to target 2025-2026 for the remaining inactivated vaccines.

In response to these recommendations, the MAH removed the influenza B/Yamagata lineage from Flucelvax Tetra and submitted a MA for the trivalent vaccine (TIVc) based on clinical evidence from TIV and QIVc. The actual vaccine composition in this submission follows recommendations for the 2024/2025 season, while the target MA and availability is intended for the season 2025-2026. This approach has been agreed by the EMA/ETF and CHMP and has been followed by other MAHs of inactivated influenza vaccines.

The clinical development program to support the registration of the trivalent version of Flucelvax (TIVc) was based on the previous development of TIVc, which was the foundation of development of the quadrivalent version of Flucelvax (QIVc) to provide prophylaxis against both Type B-lineages of influenza viruses, B/Victoria and B/Yamagata.

TIVc is a trivalent surface antigen, inactivated, influenza vaccine, prepared in Madin-Darby Canine Kidney (MDCK) cell cultures. The active substance comprises virus surface antigens (hemagglutinin [HA] and neuraminidase [NA]) of the 3 strains of influenza virus recommended by the World Health Organization (WHO) for the Northern or Southern Hemisphere season: 2 A strains (H1N1 and H3N2) and 1 B strain (Victoria lineage). The manufacturing process is the same as Flucelvax Tetra.

3.1.3. Main clinical studies

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

In addition to these studies, supportive data from 16 phase I to III studies have been performed with TIVc (Optaflu was authorised in Europe via the centralised procedure in 2007), including 12 randomised controlled studies against an egg-based licensed comparator and an absolute efficacy study in adults 18 to < 50 years (V58P13).

In addition, the MAH included immunogenicity and safety data generated with TIVc vaccine in children 4 to < 18 years in study VP58P12.

An extension of the indication was granted in 2020 to 2 years of age and above. For that procedure, the MAH presented the results from study V130_12, a Phase 3/4 efficacy, immunogenicity and safety study in children 2 to < 18 years of age.

The scope of this extension of indication application is to extend the indication to 6 months of age and above. Results from study V130_14, a Phase 3 efficacy, immunogenicity and safety study in children 6 to < 48 months of age have been submitted. Although study V130_14 has been carried out with the QIVc, the results obtained are relevant to the TIVc because the manufacturing process is the same and they have overlapping compositions.

3.2. Favourable effects

In general, the design of the phase III study conducted to evaluate efficacy, safety and immunogenicity of the QIVc in children 6 to < 48 months of age (V130_14 clinical study) is considered adequate, and therefore applicable to TIVc.

Both pre-specified success criteria for the primary endpoints were met, so absolute vaccine efficacy (aVE) was demonstrated for QIVc versus the non-influenza comparator vaccine.

For RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain, the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 41.26% (97.98% CI: 21.55, 56.02). For culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to vaccine strain the aVE of QIVc versus the comparator vaccine in subjects 6 months through 47 months of age was 46.90% (97.5% CI: 19.19, 65.11).

Moreover, aVE analyses was also performed by stratifying according to the following subgroups: age, vaccination history, race, sex, country and season. None of these analyses questioned the superior aVE of the vaccine vs the comparator.

Additionally, the vaccine has been proven to be immunogenic across different seasons, both in terms of HI and MN antibodies.

Since the only difference between QIVc and TIVc is the absence of the B/Yamagata strain and both vaccines have the same manufacturing, the data obtained with QIVc in study V130_14 supports the extension of indication for TIVc. Therefore, the data and analysis presented are considered adequate, and robust enough to support the indication for prevention of influenza in adults and children from 6 months of age and older.

3.3. Uncertainties and limitations about favourable effects

The trial did not include subjects with underlying diseases (such as respiratory, immunocompromised, etc.) who are representative of the risk groups for which the influenza vaccine is routinely recommended. However, based on previous experience with influenza vaccines, some of the underlying diseases (such as respiratory diseases that do not influence the immune response to the antigen) are not expected to impact the vaccine efficacy. On the other hand, it is noted that immune response of immunosuppressed subjects may not be optimal, but this aspect is reflected in the SmPC.

The immunogenicity of the vaccine is variable across different seasons, and although there is uncertainty regarding the low immunogenicity observed for B/Victoria strain and its effect on clinical efficacy during seasons 1 and 2, the vaccine has been proven to be immunogenic across different seasons.

3.4. Unfavourable effects

The safety assessment of the EoI of Flucelvax (TIVc) was based on the data of the completed Flucelvax Tetra vaccine (QIVc), Study V130_14. The result of this study supported the EoI from 6 months of age for Flucelvax Tetra (number procedure EMEA/H/C/004814/II/0047).

According to the data submitted in the Flucelvax Tetra Study V130_14, the percentage of subjects reporting any solicited AE after any dose of QIVc was 55.8% (32.3% of subjects reported any solicited local AEs and 40.9% any solicited systemic AEs).

The majority of solicited local and systemic AEs after any vaccination were mild or moderate in severity and were resolved in few days. The most frequently solicited local AEs were tenderness (22.3%) and erythema (19.7%), followed by induration (14%) and ecchymosis (9.3%) and the most frequently

solicited systemic AEs were irritability (21.2%), sleepiness (17.3%) and change of eating habits (15.7%), followed by diarrhoea/loose stools (13.2%) and vomiting (6.6%). Fever (≥38º) was reported by 10.9% of participants in QIVc after any dose. Severe fever (≥40º) was reported by 0.1% (4 participants after dose 1 and 2 participants after dose 2).

Comparing the incidences of solicited AEs with the control group, after vaccination 1 (QIVc or Men C vaccine), a lower incidence of solicited local AEs was observed in QIVc than in Men C, and a similar incidence in both groups regarding systemic AEs. No difference between groups was observed after vaccination 2 (QIVc or placebo).

The incidence of unsolicited AEs or related unsolicited AEs was similar between groups. In addition, the incidence of SAEs was similar and low in both groups. None of the SAEs reported in the QIVc group were assessed as related to QIVc.

Post-marketing experience with QIVc and TIVc (since it was approved) has not identified any safety concerns.

3.5. Uncertainties and limitations about unfavourable effects

There are no clinical data with TIVc in subjects aged 6 months and older, but the experience with QIVc and post-marketing data with TIVc supports the extension of indication. TIVc has the same composition and the same manufacture process as QIVc with the exception of B/Yamagata strain, which has been removed in response to a request by WHO.

It would be expected that TIVc would present the same safety profile than QIVc in subjects aged 6 months to 47 months. Therefore, a higher frequency of solicited systemic AEs (mainly irritability, sleepiness, and loose stools/diarrhoea) is likely to be observed in subjects aged 6 to 23 months of age than in 24 to 47 months of age after receiving TIVc.

3.6. Effects Table

Table 22 Effects Table for QIVc in children between 6 to 47 months

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
aVE RT-PCR confirmed influenza, Type A and/or B, regardless of antigenic match Subjects 6 to≤ 47 months	QIVc vaccine n=2856 Comparator n=2835	(97.98% CI)	41.26 (21.55, 56.02)		Primary Endpoint 1a	Study V130_14
aVE culture confirmed influenza, Type A and/or B, antigenically matched Subjects 6 to ≤ 47 months	QIVc vaccine n=2856 Comparator n=2835	(97.5% CI)	46.90 (19.19, 65.11)		Primary endpoint 1b	Study V130_14
Unfavourable Effects						
Solicited local AEs Subjects 6 to 47 months of age	QIVc vaccine, n=2857 Comparator, n=2840	Incident rate (%)	32.3% 40.4%		Secondary safety endpoint	Study V130_14
Solicited systemic AEs Subjects 6 to 47 months of age	QIVc vaccine, n=2857 Comparator, n=2840	Incident rate (%)	40.9% 42.5%		Secondary safety endpoint	Study V130_14
Unsolicited systemic AEs Subjects 6 to 47 months of age	QIVc vaccine, n=2857 Comparator, n=2840	Incident rate (%)	42.5% 45.4%		Secondary safety endpoint	Study V130_14
Related unsolicited systemic AEs Subjects 6 to 47 months of age	QIVc vaccine, n=2857 Comparator, n=2840	Incident rate (%)	4.2% 3.7%		Secondary safety endpoint	Study V130_14
SAE Subjects 6 to 47 months of age	QIVc vaccine, n=2857 Comparator, n=2840	Number of subjects and Incident rate (%)	64 (2.2%) 84 (3.0%)		Secondary safety endpoint	Study V130_14
Related SAE	QIVc vaccine,	Number	0 (0%)		Secondary safety	Study

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Subjects 6 to 47 months of age	n=2857 Comparator, n=2840	of subjects and Incident rate (%)	0 (0%)		endpoint	V130_14

Abbreviations: aVE: absolute vaccine efficacy

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The submitted efficacy data from study V130_14 demonstrate that Flucelvax Tetra is efficacious in preventing influenza in children 6 to < 48 months of age. The observed aVE against RT-PCR confirmed influenza due to any influenza Type A and/or Type B virus, regardless of antigenic match to vaccine strain in subjects 6 months through 47 months of age (primary endpoint) was 41.26% (97.98% CI: 21.55, 56.02). was, and the LL 97.98% CI was above 0%, also the observed aVE against culture confirmed influenza due to influenza Type A and/or Type B virus antigenically matched to vaccine strain the aVE in subjects 6 months through 47 months of age was 46.90% (97.5% CI: 19.19, 65.11) and the 97.5% was above 0%. All secondary endpoints were consistent with the primary study endpoint.

In terms of safety, QIVc vaccine is well tolerated and has a good reactogenicity profile in subjects aged 6 months through 47 months of age, which is similar to the known pattern in older subjects. The majority of the AEs were mild or moderate in severity and were resolved in few days after vaccination. Moreover, TIVc was authorised for use in ages 6 months and older in the US on 4 March 2024 and the post marketing experience with TIVc or QIVc indicated that no new safety concerns were identified in this population.

3.7.2. Balance of benefits and risks

Taking into consideration all the above, it is concluded that the clinical data (efficacy and safety) support the indication from 6 months of age and above for Flucelvax TIVc. The data from study V130_14 has been generated with QIVc, but the same conclusion can be reached for the TIVc, since both vaccines are manufactured using the same process and have overlapping compositions.

3.8. Conclusions

The overall benefit-risk of Flucelvax is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of children from 6 months of age and older for FLUCELVAX, based on results from study V130_14. This is a Phase III, Randomised, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine When Administrated in Healthy Subjects Aged 6 Months Through 47 Months. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. Version 4.0 of the RMP has been approved. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement changes to sections 4.4 and 4.5 of the SmPC to align them with the QRD guideline and reflect experience on co-administration with other vaccines.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion for Flucelvax Procedure No. EMEA/H/C/006532/II/0001