17 September 2020
EMA/CHMP/276144/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Flucelvax Tetra

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

Procedure No. EMEA/H/C/004814/II/0013

Marketing authorisation holder (MAH): Seqirus Netherlands B.V.

Note

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

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List of abbreviations

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

RBC Red blood cells

RT-PCR Reverse transcription polymerase chain reaction

SA Scientific advice

SAE Serious adverse event

SCR Seroconversion rate

SD Standard deviation

SOC System organ class

TIV Trivalent influenza vaccine

TIVc Cell-based, trivalent influenza vaccine

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

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

TIVe Egg-derived, trivalent, inactivated, influenza vaccine

TIVeA Egg-derived trivalent influenza vaccine (Agrippal)

TIVeF Egg-derived trivalent influenza vaccine (Fluvirin)

UK United Kingdom

US United States of America

VRBPAC FDA's Vaccine and Related Biological Products Advisory Committee

WHO World Health Organization

YOA Years of Age

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 10 March 2020 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 and IIIB

Extension of the indication of prophylaxis of influenza, from the currently approved age range "adults and children from 9 years of age" to "adults and children from 2 years of age" for Flucelvax Tetra; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics 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/0084/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002068-PIP01-16-M03 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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 applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 June 2016	EMEA/H/SA/2628/2/FU/1/2016/PED/II	Dr Hans Ovelgönne and Dr Kerstin Wickström

23 February 2017	EMEA/H/SA/2628/1/FU/1/2017/III	Prof. Fernando de Andrés Trelles and Dr Rune Kjeken

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	10 March 2020
Start of procedure:	28 March 2020
CHMP Rapporteur Assessment Report	19 May 2020
PRAC Rapporteur Assessment Report	29 May 2020
PRAC members comments	03 June 2020
Updated PRAC Rapporteur Assessment Report	04 June 2020
PRAC Outcome	11 June 2020
CHMP members comments	15 June 2020
Updated CHMP Rapporteur Assessment Report	18 June 2020
Request for Supplementary Information	25 June 2020
Rapporteur's preliminary assessment report circulated on:	14 August 2020
Joint Rapporteur's updated assessment report circulated on:	10 September 2020
CHMP opinion:	17 September 2020

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 characterized by the abrupt onset of respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis. The disease presents as a non-specific systemic illness which may be complicated by a range of viral or bacterial infections. Clinical manifestations are generally consistent across adult and paediatric populations, however variability in clinical presentation may occur within or between adult, older adult or paediatric age groups, and some

manifestations may be age-specific, such as irritability in young children. Fever tends to be less frequent and less pronounced in older adults compared with adults and children.

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

State the claimed the therapeutic indication

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

Epidemiology and risk factors, screening tools/prevention

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

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

The difficulty of choosing the correct B lineage to include in influenza vaccine formulations raises the possibility of a mismatch between the influenza B strain contained in the influenza vaccine and the influenza B strain predominantly circulating in the community in any given season, which for the northern hemisphere seasonal influenza vaccines occurred in 5 of the 10 influenza seasons 2001/2002 to 2010/2011. In order to avoid vaccine mismatch, quadrivalent influenza vaccines that include influenza B strains from both lineages have been recommended and these are expected to provide protection against the additional B strain. The first QIV was approved in the United States of America (US) prior to the 2012/13 Northern Hemisphere influenza season. A US study estimated that, in a season with a B strain mismatch, availability of quadrivalent influenza virus vaccines could reduce annual influenza cases (range: 2200–970,000), hospitalizations (range: 14–8200), and deaths (range: 1–485) in the US.

QIVc is a quadrivalent vaccine including B strains of both lineages and is therefore expected to improve protection in target populations, especially in children where significant disease due to influenza B strains occurs and the potential for vaccine B strain mismatch has existed with trivalent influenza virus vaccines.

QIVc is manufactured through cell-based manufacturing processes that are consistent with those used for the US-approved TIVc, Flucelvax, and the formerly (until June 2017) EU-approved TIVc, Optaflu.

Aetiology and pathogenesis

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

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

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.

The protection afforded by conventional inactivated influenza vaccines is driven by how well the strains in the vaccine match the viruses that circulate during influenza season (antigenic match).

2.1.2. About the product

QIVc is a quadrivalent surface antigen, inactivated, influenza vaccine, prepared in Madin Darby Canine Kidney (MDCK) cell cultures. The active substance comprises virus surface antigens (hemagglutinin and neuraminidase) of the 4 strains of influenza virus recommended annually by the WHO for the Northern Hemisphere season:

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

- a strain B (Victoria lineage).

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

The cell-based production process of "on demand" suspensions of cells 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. QIVc is produced using the same cell culture manufacturing platform as TIVc.

TIVc was approved in the EU in June 2007, under the tradename of Optaflu. One 0.5 mL dose of TIVc contains approximately 15 µg HA from each of the 3 influenza strains – A/H1N1, A/H3N2 and B (either Victoria or Yamagata lineage). TIVc was approved by the FDA in November 2012, for use in adults ≥18 years of age. The age indication for the US-licensed TIVc was extended in May 2016 for use in children ≥4 years of age.

QIVc was approved in the US in May 2016 via the accelerated approval pathway for use in adults and children of ≥4 years, with the post-approval requirement to conduct a paediatric absolute efficacy study. QIVc is currently approved in the EU, under the name of Flucelvax Tetra, since December 2018, for the prophylaxis of influenza in adults and children from 9 years of age.

QIVc and TIVc were originally developed and marketed by Novartis Vaccines and Diagnostics GmbH (NVD). In December 2016 the marketing authorisation for Optaflu was transferred to Seqirus GmbH. The registration for Optaflu expired in June 2017 for commercial reasons, so TIVc is no longer authorised in Europe.

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

Study V130_12 was conducted in 8 countries (Australia, Philippines, Thailand, Estonia, Finland, Lithuania, Poland and Spain) over 3 influenza seasons (Southern Hemisphere 2017 [Season 1], Northern Hemisphere 2017-2018 [Season 2], and Northern Hemisphere 2018-2019 [Season 3]). The study is registered with EudraCT (2016-002883-15) and the results were submitted within 6 months of the 30 September 2019 end of study date, in accordance with Article 46 of the Paediatric Regulation (EC) No. 1901/2006. The design of V130_12 has been previously discussed with EMA at meetings held in 2016 and 2017, and it was also discussed during paediatric investigation plan (PIP) with PDCO.

The V130_12 study was conducted in accordance with the CBER Guidance for Industry: Clinical data needed to support the licensure of seasonal inactivated influenza vaccines (CBER 2007) and the EMA Guideline on Influenza Vaccines Non-clinical and Clinical Modules (EMA/CHMP/VWP/457259/2014). The study fulfils the product's US FDA postmarketing study requirement (PMR No. 1) to demonstrate absolute vaccine efficacy (aVE) in children 4 to < 18 years of age. In addition, children ≥2 years of age were enrolled in this study to further evaluate QIVc in a broader age range and to support submissions in various global regions.

2.1.4. General comments on compliance with GCP

The MAH states that clinical study V130_12 was designed, implemented, and reported on in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, 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.

The study was conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements.

No GCP inspections are considered necessary.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

QIVc was initially granted marketing approval in the US for use in persons 4 years of age and older on 23 May 2016. Marketing authorisation was also granted for QIVc in Europe in December 2018 and in Canada in November 2019 for use in people 9 years and older and in Brazil for use in people 18 years and older in February 2020. Approval was based on non-inferior immunogenicity and safety of QIVc against the trivalent formulation of the vaccine TIVc, in adults (V130_01) and children 4 to < 18 years of age (V130_03) and demonstration of efficacy of the trivalent formulation (V58P12) in adults and immunogenicity in children 3 to < 18 years of age (V58P13).

While the US FDA considered QIVc approved in adults without a further postmarketing requirement, approval in children between 4 and < 18 years of age was granted in accordance with the US regulations for accelerated approval. Final approval under these regulations was dependent on successful demonstration of the clinical benefit in an adequate and well-controlled clinical trial in children 4 to < 18 years of age. The design of the V130_12 postmarketing requirement study was revised to include children 2 to < 4 years of age to also support the registration of the vaccine in children 2 years and older in other regions globally.

When the marketing authorisation was submitted for QIVc in Europe in December 2018, the indication sought by the MAH was the prevention of influenza in children 4 years of age and older and adults.

The following studies were presented to support the claimed indication:

- Two phase III studies conducted to evaluate the safety and efficacy (immunogenicity) of the QIVc in children 4 to < 18 years of age (V130_03 study) and in adults 18 to > 75 years of age (V130_01 study).
- Supportive data on absolute vaccine efficacy obtained from TIVc (study V58P13 in adults 18-49YOA), and additional supportive immunogenicity data obtained with TIVc vaccine (V58P12 in children 3-18YOA).
- To provide, as a post-approval commitment, the data from an additional efficacy study (V130_12) including subjects from 2 to < 18 years of age, which was ongoing at the time of MAA, to support

the claimed indication from 4 to <18 years of age. The conduction of this study was a commitment (for both FDA and CHMP) to approve the current clinical data package.

Upon assessment of these data the adult indication was granted without any issue. Regarding the paediatric indication (4 to 18 years of age), the CHMP was not convinced that the data presented at that moment were sufficiently conclusive, and thus the CHMP requested the Vaccine Working Party (VWP) to address this issue before reaching a conclusion on the Flucelvax Tetra application.

No efficacy data were generated with QIVc in any age group. Therefore, in order to support a conclusion on the likely efficacy of QIVc in the paediatric population aged 4-<18 years, the MAH proposed an immunobridging approach. In principle, this indirect immunobridging approach was considered valid by the VWP. But in the group aged 4 to <9 YOA, the co-primary objective of this non-inferiority study was not met for the GMT ratios and SCRs against A/H3N2 when sera were tested with the cell-based antigen HI assay. When egg-base antigens were used in the HI assay to test the same sera, immune responses to the A/H3N2 and B strains did not meet the non-inferiority criteria.

Overall, the VWP considered there were some remaining uncertainties regarding the adequacy of the immune responses to A/H3N2 and B strains documented in the study used for non-inferior comparisons in the age subset 4 to 8 years. The VWP was not convinced that the available immunogenicity data could support approval in this age group.

As a result of the assessment, the indication granted for the initial marketing authorisation included adults and children 9 years of age and above.

Within this application, the MAH has now submitted the results of the V130_12 study, in support of an indication for prevention of influenza in adults and children from 2 years of age and older. These results provide data from clinical study V130_12 (NCT03165617), a Phase 3/4 efficacy, immunogenicity and safety study in children 2 to < 18 years of age to support the extension of the indication of QIVc for prevention of influenza in adults and children from 2 years of age. The design of V130_12 was previously discussed with EMA at meetings held in 2016 and 2017, and it was also discussed during paediatric investigation plan (PIP) negotiations with PDCO.

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_12 Clinical Study Design

Study No. **Countries (No. of Sites)** **Influenza Season**	**Study Design** **(Licensed Control)** **[assay used for efficacy/ immunogenicity objectives]**	**No. of Subjects Enrolled / Completed Protocol**	**Characteristic and Age of Subjects**	**Vaccination Schedule** **(IM doses)**	**Objectives**
V130_12 Australia (2), Estonia (5), Finland (10),	Phase 3/4, randomized, observer blinded, controlled	QIVc: 2258/2249	Healthy subjects age 2 years to < 18 years of age at the	Not previously vaccinated[1] 2 to < 9 yrs:	Absolute vaccine efficacy, immunogenicity, safety

Lithuania (6), Philippines (7) Poland (6), Spain (1), Thailand (2). SH 2017 NH 2017/2018 NH 2018/2019	(Menveo Meningococcal Conjugate Vaccine) [RT-PCR and viral culture for efficacy objectives; HI and MN assays for immunogenicity objectives]	Comparator: 2256/2247	time of enrolment	2 vaccinations of 0.5 mL, 28 days apart Previously vaccinated[1] 2 to < 9 years or 9 to < 18 years: 1 vaccination of 0.5 mL	

Source: Section 5.3.5.1, CSR V130_12
Abbreviations: HA = hemagglutinin; HI = hemagglutination inhibition; IM = intramuscular MN = microneutralization; NH = Northern Hemisphere; No. = number; QIVc = cell-derived quadrivalent subunit influenza virus vaccine; RT-PCR = reverse transcription polymerase chain reaction; SH = Southern Hemisphere.
Note 1: Previously vaccinated subjects under 9 years of age and all subjects 9 to < 18 years received 1 study vaccination (QIVc or comparator) on Day 1. For subjects under 9 years of age who had not been previously vaccinated, 2 study vaccinations were administered separated by 28 days; the comparator vaccine group received comparator on Day 1 followed by a saline placebo vaccine on Day 29, whereas the QIVc group received 2 QIVc vaccinations on Days 1 and 29.

2.3.2. Pharmacokinetics

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

2.3.3. Pharmacodynamics

Mechanism of action

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

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

2.3.4. Discussion on clinical pharmacology

In Study V130_12, immunogenicity endpoints were assessed by the haemagglutination inhibition (HI) and microneuralization (MN) assay for all strains.

The HI assay used for immunogenicity evaluation of influenza vaccines is considered adequate for the V130_12 QIVc study, because it is in line with the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014). The MAH states that in recent years it has been observed that H3 viruses have decreased replicative capacity on MDCK cells and can poorly agglutinate RBC of different species. Therefore, an alternative method for the antigenic typing of H3 viruses was developed based on the ViroSpot methodology and detection of viral NP protein rather than agglutinating activity. This assay can be used for the typing and subtyping of influenza. The qualitative ViroSpot assay for antigenic typing that were used for typing H3N2 isolates is based on a quantitative microneutralization assay. As

performed for antigenic typing of Influenza viruses using the conventional HI assay, the MN titres obtained from the viruses isolated from clinical specimens were compared to the MN titre obtained with the reference vaccine strain when using a ferret anti-serum obtained from an animal infected with the reference vaccine strain. The ViroSpot for antigenic matching is a qualitative assay and its output is either a non-matching, "UNMATCH" or matching, "MATCH" status compared to the reference corresponding vaccine strain.

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

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

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.

Since the QIVc is propagated in a mammalian cell line rather than in embryonated hens' eggs (differently than the conventional influenza vaccines), it is considered adequate that the HI assays had been performed using test antigens propagated in MDCK cells (mammalian cell culture-derived test antigens) rather than antigens from virus grown in eggs.

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.

Two validation reports of the HI test were included in the variation application. All validations were carried out according to ICH guidelines Q2A and Q2B, and covered additional strains of the four seasonal influenza virus types H3N2, H1N1, B Yamagata and B Victoria. The parameters assessed were precision, format variability, dilutional linearity, relative accuracy, specificity and lower limit of quantification. 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, two validation reports of the MN test were included in the variation application. All validations were carried out according to ICH guidelines Q2A and Q2B, and covered additional strains of the four seasonal influenza virus types H3N2, H1N1, B Yamagata and B Victoria. The parameters assessed were precision, format variability, dilutional linearity, relative accuracy, specificity and lower limit of quantification. 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. This aspect was discussed with PDCO and has been agreed as part of the PIP.

The explanation of the observed problem and the solution implemented are satisfactory.

2.3.5. Conclusions on clinical pharmacology

No clinical pharmacology studies were performed in the clinical development program to support the extension of indication of Flucelvax Tetra. This approach is endorsed due to the nature of the product under evaluation.

The haemagglutination inhibition (HI) assay used for immunogenicity evaluation of influenza vaccines is considered adequate for the V130_12 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 2 (A/Singapore/GP2050/2015), 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 have been well addressed.

2.4. Clinical efficacy

2.4.1. Dose response study

Vaccine dosage and schedule

In clinical Study V130_12 carried out in children 2 to < 18 years of age, QIVc was administered as a 0.5mL intramuscular injection in either a single or two dose vaccination regimen. The vaccination regimen for each subject was determined on the basis of the subject's age and previous influenza vaccination history, according to the US Advisory Committee on Immunization Practices (ACIP) paediatric influenza vaccine dosing recommendations (Grohskopf et al., 2015), and other international dosing recommendations for seasonal influenza vaccines.

Vaccine Formulation

The influenza viral strains used in the vaccines of the QIVc clinical trial (CT) complied with the annual recommendations made by the WHO (WHO 2013) at the time the trial was performed, and were also the same recommended by the FDA's Vaccine and Related Biological Products Advisory Committee (VRBPAC) in the US and by the CHMP in the EU.

Dose-response studies

The dose-finding studies were conducted for the initial submission.

Conclusion on the dose-response study

Within this application, 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. This is considered acceptable.

2.4.2. Main study

This application includes data for children 2 to < 18 years of age, in Study V130_12, to seek approval for use of QIVc in children 2 years of age and older.

Study V130_12: A Phase III/IV, Stratified, Randomized, Observer Blind, Multicentre Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥2 Years to <18 Years of Age

Methods

Study participants

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

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

Subject Characteristics and Main Criteria for Inclusion and Exclusion

Inclusion Criteria

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

Exclusion Criteria

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

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

Treatments

The two treatments consist of one tetravalent QIVc and a non-influenza vaccine (Meningococcal ACWY vaccine, Menveo). The placebo for subjects in both groups, who were not previously vaccinated and received a second vaccination for blinding purposes, was a 0.9% saline for injection, clear, colourless

liquid. The dose administered was 0.5 ml. Vaccination was performed intramuscularly, preferably in the deltoid muscle of the non-dominant arm.

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

Objectives

Primary Efficacy Objective:

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

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

Co-Primary Efficacy Objective: to demonstrate the aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR- or culture- confirmed influenza, due to any influenza Type A and B strain in subjects 3 to <18 years of age. The success criterion used for this co-primary objective was as follows: The efficacy of the QIVc was demonstrated if the LL of the 2-sided 95% CI for VE was above 30%.

Secondary Efficacy Objectives:

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

1. to demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR- or culture-confirmed influenza due to any influenza Type A and B strain.
2. to demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of RT-PCR-confirmed influenza due to any influenza Type A and B strain.
3. to demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of culture-confirmed influenza due to any influenza Type A and B strain.
4. to demonstrate aVE of QIVc versus a non-influenza comparator determined by the first occurrence of culture-confirmed influenza caused by influenza strains antigenically matched to the strains selected for the seasonal vaccine.

Secondary Immunogenicity Objective:

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

Exploratory Efficacy Objective:

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

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

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

Exploratory Immunogenicity Objective:

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

Outcomes/endpoints

Efficacy

Primary Efficacy Endpoints:

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

Secondary Efficacy Endpoints:

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

Exploratory Efficacy Endpoints:

- For exploratory efficacy objective 1:
  - number of deaths as derived from serious adverse event (SAE) forms
  - number of subjects with pneumonia as derived from AE forms
  - number of subjects with physician-confirmed otitis media as derived from AE forms
- For exploratory efficacy objective 2: the time from the last study vaccination to the onset of the first

occurrence of culture-confirmed influenza, due to any influenza H3N2 virus strains antigenically matched to the influenza H3N2 A/Singapore/GP2050/2015 (cell seed) strain, occurring at >14 days after the last vaccination and until the end of the influenza season.

Immunogenicity

Secondary Immunogenicity Endpoints:

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

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

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

Sample size

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

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

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

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

Assuming a true vaccine efficacy of 50% it was calculated that approximately 381 observed confirmed ILI cases would be needed to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30% with approximately 90% power. The statistical test performed will depend only on number of

confirmed ILI cases (events), so sample size estimate is only for operational reasons. Estimated sample size to arrive at 381 events, is 6,350 evaluable subjects (or 3,175 evaluable subjects per treatment group), assuming attack rate in non-influenza comparator vaccine subjects of 8%, assumed vaccine efficacy of 50%, VE is greater than 30%, and the risk of infection contained entirely within period covered by follow-up. Accounting for early dropout and uncertainty about the assumed parameters, 7,056 subjects are planned to be enrolled to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30%.

Table 2 summarizes the power calculations assumptions and the number of events required to meet primary and co-primary endpoint.

Table 2: Power calculation for Primary and Co-primary endpoints

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

*accounted for early dropout and uncertainty

Randomisation

A total of 4514 subjects 2 to <18 years of age were enrolled and randomized in a 1:1 ratio to QIVc or non-influenza comparator vaccine, Menveo, a Neisseria meningitidis serogroup A, C, W-135, Y conjugate vaccine. The randomization was stratified by age (2 to < 9 years and 9 to < 18 years). Subjects between 2 to < 9 years of age were further stratified by previous influenza vaccine status. Study subjects were scheduled to receive either a single dose of 0.5 mL of the study vaccine or a two dose study vaccination regimen separated by approximately 4 weeks as clinically indicated depending on age and previous influenza vaccination history according to paediatric influenza vaccine dosing recommendations (Grohskopf et al., 2015) and consistent with international guidelines.

Blinding

This trial was designed as an observer blind study.

Statistical methods

Analysis Sets:

- Full Analysis Set (FAS) Efficacy: All subjects in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination.
- FAS Immunogenicity: All subjects in the All Enrolled Set, immunogenicity subset who received at least one dose of study vaccine and provided evaluable serum samples at both baseline and after the last vaccination.
- Per Protocol Set (PPS) Efficacy/Immunogenicity Set: All subjects in the FAS Efficacy / Immunogenicity who:
    - Correctly received the vaccine (i.e., received the vaccine to which the subject was randomized and at the scheduled time point[s]).
    - Had no protocol deviations leading to exclusion as defined prior to unblinding / or analysis.
    - Were not excluded due to other reasons (e.g., subjects who withdrew informed consent) as defined prior to unblinding or analysis.
- Solicited Safety Set (Solicited Local and Systemic Adverse Events and Other Solicited Adverse Events): All subjects in the Exposed Set who had gone through any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics.
- Unsolicited Safety Set (Unsolicited Adverse Events): All subjects in the Exposed Set who had gone through any AE assessments, i.e., a subject did not have to have any AEs to be included in this population.
- Overall Safety Set: All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

Analysis of Efficacy:

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

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

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

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

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

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

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

Immunogenicity:

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

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

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

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

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

Results

Participant flow

A total of 4514 subjects were enrolled in Study V130_12. The population used for the efficacy analysis was the Efficacy Full Analysis Set (FAS) which included all enrolled subjects that were randomized, received at least one study vaccination and provided efficacy data. Five enrolled subjects were excluded from the Efficacy, FAS population. Efficacy analysis were repeated with the Efficacy Per Protocol Set (PPS) which included all FAS subjects that correctly received the vaccines, had no protocol deviations leading to exclusion and were not excluded due to other reasons defined prior to unblinding or analysis. In total, 9 (0.4%) subjects in the QIVc group and 9 (0.4%) subjects in the comparator group were withdrawn from the study. The number of enrolled subjects and disposition by age cohort and study treatment are shown in Figure 1.

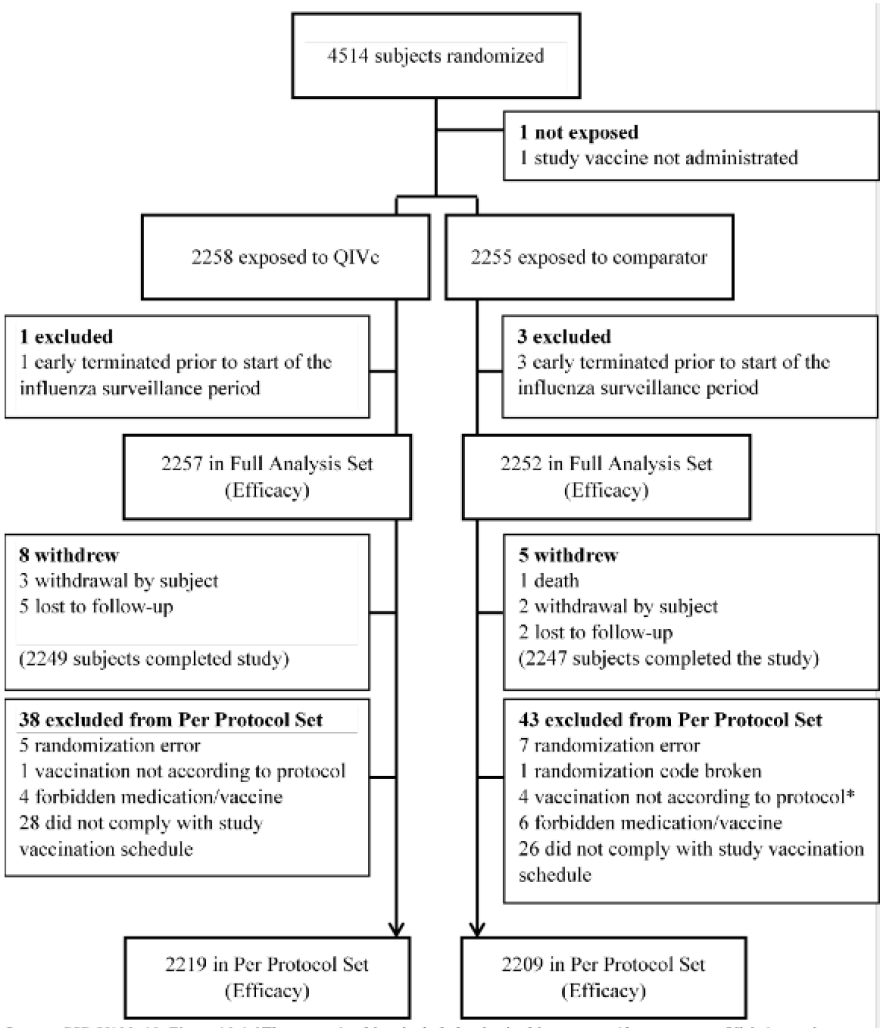

Figure 1: Study V130_12 subject allocation flowchart

Recruitment

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

Conduct of the study

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

Table 3: Summary of study terminations in subjects 2 to <18 years of age – All enrolled, study V130_12

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

Baseline data

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

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

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

Table 4: Demographics and baseline characteristics – All Enrolled Set

	QIVc N=2258	Comparator N=2256	Total N=4514
Age (years)			
n	2258	2256	4514
Mean (SD)	8.7 (4.0)	8.9 (4.1)	8.8 (4.1)
Age Group (n[%])			
2 to < 18 years	2258 (100.0)	2256 (100.0)	4514 (100.0)
3 to < 18 years	2209 (97.8)	2205 (97.7)	4414 (97.8)
4 to < 18 years	2046 (90.6)	2036 (90.2)	4082 (90.4)
9 to < 18 years	1112 (49.2)	1113 (49.3)	2225 (49.3)
2 to <4 years	212 (9.4)	220 (9.8)	432 (9.6)
2 to < 9 years	1146 (50.8)	1143 (50.7)	2289 (50.7)
Sex (n[%])			
N	2258	2256	4514
Male	1152 (51.0)	1174 (52.0)	2326 (51.5)
Female	1106 (49.0)	1082 (48.0)	2188 (48.5)
Race (n[%])			
N	2258	2256	4514
American Indian or Alaska Native	0	0	0
Asian	1106 (49.0)	1100 (48.8)	2206 (48.9)
Black or African American	1 (<0.1)	0	1 (<0.1)
Native Hawaiian or Other Pacific Islander	0	2 (0.1)	2 (<0.1)
White	1140 (50.5)	1139 (50.5)	2279 (50.5)
Other	11 (0.5)	15 (0.7)	26 (0.6)
Ethnic Origin (n[%])			
n	2258	2256	4514
Hispanic or Latino	11 (0.5)	11 (0.5)	22 (0.5)
Not Hispanic or Latino	2245 (99.4)	2245 (99.5)	4490 (99.5)
Not Reported	2 (0.1)	0	2 (<0.1)
Unknown	0	0	0

	QIVc N=2258	Comparator N=2256	Total N=4514
Country (n[%])			
n	2258	2256	4514
Australia	96 (4.3)	99 (4.4)	195 (4.3)
Estonia	599 (26.5)	599 (26.6)	1198 (26.5)
Finland	168 (7.4)	158 (7.0)	326 (7.2)
Lithuania	142 (6.3)	150 (6.6)	292 (6.5)
Philippines	902 (39.9)	898 (39.8)	1800 (39.9)
Poland	147 (6.5)	151 (6.7)	298 (6.6)
Spain	3 (0.1)	2 (0.1)	5 (0.1)
Thailand	201 (8.9)	199 (8.8)	400 (8.9)
Previous Influenza Vaccination (n[%])			
n	2258	2256	4514
Previously vaccinated	1488 (65.9)	1487 (65.9)	2975 (65.9)
Not previously vaccinated	770 (34.1)	769 (34.1)	1539 (34.1)
Season (n[%])			
n	2258	2256	4514
Season 1	1199 (53.1)	1196 (53.0)	2395 (53.1)
Season 2	459 (20.3)	460 (20.4)	919 (20.4)
Season 3	600 (26.6)	600 (26.6)	1200 (26.6)
Body Mass Index (kg/m^2)			
n	2258	2255	4513
Mean (SD)	17.5 (3.7)	17.6 (3.8)	17.6 (3.7)
Median	16.5	16.5	16.5

Source: Section 5.3.5.1, CSR V130_12 Table 10-6

Abbreviations: QIVc = cell-derived quadrivalent subunit influenza virus vaccine; SD = standard deviation.

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

Numbers analysed

Efficacy Population, Study V130_12

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

Immunogenicity Population, Study V130_12

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

The subject populations are presented in the following table:

Table 5: Overview of efficacy and immunogenicity sets analysed – as randomised

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

Source: Table 14.1.1.1 and Table 14.1.1.1.1.

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

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

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

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

Outcomes and estimation

EFFICACY

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

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

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

In the FAS Efficacy, for 539 of the 4509 subjects 2 to < 18 years of age RT-PCR- or culture-confirmed influenza caused by any Type A or Type B strain were observed, i.e., in 175 subjects in the QIVc group (7.8%) and 364 subjects in the comparator group (16.2%) (Table 6).

The analysis shows that QIVc prevented RT-PCR or culture confirmed influenza caused by any Type A or B strain in subjects 2 to < 18 years of age (primary efficacy endpoint) and 3 to < 18 years of age (co-primary endpoint). The VE of QIVc in children 2 to < 18 years of age was 54.6% (95% CI: 45.7 to 62.1). The success criterion was met as the LL of the 2-sided 95% CI was above 20%. The VE of QIVc in children 3 to < 18 years of age was 54.0% (95% CI: 44.8 to 61.7). The success criterion was met as the LL of 95% CI for VE is above 30% (Table 6).

Table 6: Number of subjects with first-occurrence RT-PCR-confirmed or culture-confirmed influenza and absolute vaccine efficacy (95% CI), Overall in subjects 2 to <18 Years of age and 3 to <18 years of age – FAS Efficacy

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

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

Subjects 2 to <4 years of age: In subjects 2 to <4 years of age, the overall VE of QIVc against RT-PCR- or culture-confirmed influenza was **62.66% (95% CI: 38.06; 77.49).** For further details see table 7.

Subjects 4 to <18 years of age: In subjects 4 to <18 years of age, the overall VE of QIVc against any RT-PCR- or culture- confirmed influenza was **53.33% (95% CI: 43.38; 61.54).** For further details see table 7.

Table 7(1): Number of subjects with first-occurrence RT-PCR-confirmed or culture-confirmed influenza and absolute vaccine efficacy (95% CI), Overall and by strain, in subjects 2 to <4 Years of age and 4 to <18 years of age – FAS Efficacy

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

Table 7(2): Number of subjects with first-occurrence RT-PCR-confirmed or culture-confirmed influenza and absolute vaccine efficacy (95% CI), Overall and by strain, in subjects 2 to <4 Years of age and 4 to <18 years of age – FAS Efficacy

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

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

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

[a] Adjusted aVE is presented.

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

Subjects 2 to <9 years of age: In subjects 2 to <9 years of age, the overall VE of QIVc against any RT-PCR- or culture- confirmed influenza was 50.51% (95% CI: 38.43; 60.22). These results are detailed in the following Table 8.

Subjects 9 to <18 years of age: In subjects 9 to <18 years of age, the overall VE of QIVc against any RT-PCR- or culture-confirmed influenza was 61.85% (95% CI: 47.37; 72.34). See results in the following Table 8.

Table 8(1): Number of subjects with first-occurrence RT-PCR-confirmed or culture-confirmed influenza and absolute vaccine efficacy (95% CI), Overall and by strain, in subjects 2 to <9 Years of age and 9 to <18 years of age – FAS Efficacy

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

Table 8(2): Number of subjects with first-occurrence RT-PCR-confirmed or culture-confirmed influenza and absolute vaccine efficacy (95% CI), Overall and by strain, in subjects 2 to <9 Years of age and 9 to <18 years of age – FAS Efficacy

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

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

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

[a] Adjusted aVE is presented.

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

VE estimates for the 2 to < 18 and 3 to < 18 years of age groups related to the secondary efficacy endpoints (RT-PCR-confirmed, culture-confirmed, matched) are also presented in Table 9. Additionally, VE estimates against culture-confirmed antigenically unmatched to the vaccine strains are included.

Secondary Efficacy Objective 1: Vaccine Efficacy for RT-PCR- or Culture-Confirmed Influenza Regardless of Antigenic Match – By Strain Type and Age. Out of the 539 subjects with a RT-PCR- or culture confirmed influenza caused by any Type A or Type B strain, there were 310 episodes caused by Type A and 231 caused by Type B. See table 9.

Secondary Efficacy Objective 2: Vaccine Efficacy for RT- PCR-Confirmed Influenza Regardless of Antigenic Match. The estimates of the overall VE of QIVc against RT-PCR- or culture-confirmed influenza in

comparison to the estimates of the overall VE against RT-PCR confirmed influenza are similar. The strain specific VE estimates differ slightly as the RT-PCR method was unable to determine the strain type of 29 influenza Type A strains, and therefore there were fewer Type A/H1N1 and Type A/H3N2 results by this method (Table 9).

Secondary Efficacy Objective 3: Vaccine Efficacy for Culture-Confirmed Influenza Regardless of Antigenic Match. In subjects 2 to < 18 and 3 to < 18 years of age, absolute vaccine efficacy of QIVc versus the comparator was demonstrated as determined by the first occurrence of culture-confirmed influenza due to any influenza Type A and B strains regardless of antigenic match (Table 9).

Secondary Efficacy Objective 4: Vaccine Efficacy for Culture-Confirmed Influenza Antigenically Matched. In subjects 2 to < 18 years of age, absolute vaccine efficacy of QIVc versus the comparator was demonstrated as determined by the first occurrence of culture-confirmed influenza due to antigenically matched influenza Type A and B strains. No differences were observed between subjects 2 to < 18 years of age and 3 to < 18 years of age. (See Table 9).

Table 9(1): Number of subjects with first-occurrence RT-PCR-confirmed or culture-confirmed influenza and absolute vaccine efficacy (95% CI), Overall and by strain, in subjects 2 to <18 Years of age and 3 to <18 years of age – FAS Efficacy

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

Table 9(2): Number of subjects with first-occurrence RT-PCR-confirmed or culture-confirmed influenza and absolute vaccine efficacy (95% CI), Overall and by strain, in subjects 2 to <18 Years of age and 3 to <18 years of age – FAS Efficacy

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

Other Efficacy Endpoints

The exploratory evaluation of QIVc efficacy to prevent the 2 pre-specified complications of influenza, pneumonia and otitis media, was inconclusive [LL of the 2-sided 95% CI encompassing zero]. Number of subjects with first occurrence pneumonia and otitis were derived from AE forms and reported as medically

attended AE reported within 30 days after ILI onset. The VE of QIVc relative to non-influenza comparator to prevent all-cause pneumonia and all-cause otitis media was not statistically significant.

Table 10: Summary of vaccine efficacy for first-occurrence of all-cause pneumonia and otitis media occurring at >14 days after the last vaccination AND until the end of the influenza season in subjects 2 to <18 years of age – FAS Efficacy

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

Source: Table 14.2.0.7.1.1 and Table 14.2.0.7.1.2.

IMMUNOGENICITY

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

SECONDARY PRIMARY OBJECTIVE:

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

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

The vaccine strain composition changed between seasons. Except for the Type A/H1N1 vaccine strain, all other vaccine strains (Type A/H3N2, Type B/Yamagata and Type B/Victoria) were updated. Therefore, all the immunogenicity results are presented by season, even in the case where the strain did not change (i.e. A/H1N1). For each assay and strain, the following measures were derived: GMTs, GMR, seroconversion rates, and the percentages of subjects with HI titres ≥1:40. Immunogenicity was analysed descriptively and no success criteria were applied.

HI Geometric Mean Titres and Geometric Mean Ratios

The GMTs at Days 1, and 22/50 and GMR by vaccine groups are presented in Table 11. The GMT showed that:

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

- The GMTs at Day 1 against Type B/Yamagata were higher in Season 3 compared with Season 2 (prevaccination GMTs, Season 2: 10.87 [QIVc], 12.17 [comparator] versus Season 3: 23.98 [QIVc] and 27.33 [comparator]).

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

The GMR showed:

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

Consistent with the GMT results, post-vaccination HI titres were significantly higher in the QIVc group versus the comparator group for all strains (Table 11). The results obtained for PPS Immunogenicity were consistent with results obtained in the FAS.

Percentage of Subjects with an HI Titre ≥1:40

Table 11 presents the proportion of subjects with HI titres ≥1:40 at Day 1 and Day 22/50 in the FAS Immunogenicity analysis.

- Overall there were no differences in subjects with HI titres ≥1:40 at Day 1 between QIVc and the comparator.
- Across seasons, the percentage of subjects with HI titres ≥1:40 at Day 1 were lowest against Type B/Victoria and Type B/Yamagata compared to the Type A/H1N1 and Type A/H3N2.
- The percentage of subjects with HI titres ≥1:40 at Day 1 against Type A/H1N1 and Type B/Victoria were comparable between Season 2 and 3.
- The percentage of subjects with HI titres ≥1:40 at Day 1 against Type A/H3N2 were higher for Season 2 compared to Season 3 (percentage of subjects with HI titres ≥1:40 at Day 1, Season 2: 93.3% [QIVc], 91.5% [comparator] versus Season 3: 27.9% [QIVc], 26.9% [comparator]).
- The percentage of subjects with HI titres ≥1:40 at Day 1 against Type B/Yamagata were higher in Season 3 compared to Season 2 (percentage of subjects with HI titres ≥1:40 at Day 1, Season 2: 18.6% [QIVc], 20.3% [comparator] versus Season 3: 44.8% [QIVc], 49.0% [comparator]).
- The percentages of subjects that achieved a HI antibody titre ≥ 1:40 at Day 22/50 were higher in Season 3 (94.8% [Type A/H1N1], 74.0% [A/H3N2], 68.8% [Type B/Victoria] and 79.2% [B/Yamagata]) compared with Season 2 (88.6% [Type A/H1N1], 90.0% [A/H3N2], 54.3% [Type B/Victoria] and 63.8% [B/Yamagata]).

The results obtained for PPS Immunogenicity were consistent with results obtained in the FAS Immunogenicity.

Seroconversion Rate

Table 11 summarizes the seroconversion rate post-vaccination (21 days after last vaccination, e.g., Day 22/50) in the FAS Immunogenicity.

The seroconversion rate in the QIVc group was higher as compared to the comparator group post-vaccination for all four strains. The LL of the 2-sided 95% CI for the proportion of subjects achieving an HI antibody seroconversion exceeded 30%, except for Type A/H3N2 in Season 2 (13.97%). The technical

challenges with HI assay used to assess immunogenicity against A/Singapore/GP2050/2015 (H3N2) may have contributed to the reduced rates of seroconversion in Season 2 compared with the other strains (see explanation below).

Similar results were observed for subjects in the PPS Immunogenicity.

Type A/H3N2 responses

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

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

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

Table 11: Postvaccination GMT, GMR, and percentage of subjects 2 to <9 years of age with seroconversion and HI titer ≥1:40, with 95% Cis, 21 Days After Last Vaccination (Day 22 or Day 50) – FAS Immunogenicity HI

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

Table 12: Postvaccination GMT, GMR, and percentage of subjects 2 to <9 years of age with seroconversion, with 95% CIs, 21 Days After Last Vaccination (Day 22 or Day 50) – FAS Immunogenicity MN

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

Ancillary analyses

Persistence of antibody response

Study V130_12 was not specifically designed to collect long-term efficacy or tolerance data.

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_12

Title: A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥2 years to <18 Years of Age	
Study identifier	Protocol V130_12 EudraCT 2016-002883-15 NCT 03165617
Design	Stratified, Randomized, Observer-blind, Comparator Controlled, Multicenter Study

	Duration of main phase: Duration Run-in phase: Duration Extension phase:		Day 1 through Day 180/209* or end of influenza season, whichever is longer * depending upon previous vaccination status Not applicable Not applicable
Hypothesis	Superiority (Absolute Vaccine Efficacy)		
Treatments groups	QIVc: cell-derived quadrivalent influenza vaccine		Season 1 [Southern Hemisphere 2017]: Strain Type A/Singapore/GP1908/2015 IVR-180 (H1N1) Strain Type A/HongKong/4801/2014 (H3N2) Strain Type B/Utah/9/2014 (B Yamagata) Strain Type B/HongKong/259/2010 (B Victoria) Season 2 [Northern Hemisphere 2017-2018]: Strain Type A/Singapore/GP1908/2015 IVR-180 (H1N1) Strain Type A/Singapore/GP2050/2015 (H3N2) Strain Type B/Utah/9/2014 (B Yamagata) Strain Type B/HongKong/259/2010 (B Victoria) Season 3 [Northern Hemisphere 2018-2019]: Strain Type A/Singapore/GP1908/2015 IVR-180 (H1N1) Strain Type A/North Carolina 04/2016 (H3N2) Strain Type B/Singapore/INFTT-16-06 10/2016 (B Yamagata) Strain Type B/Iowa/06/2017 (B Victoria) 1 or 2 doses depending upon previous vaccination status and/or age
	Comparator: Non-Influenza vaccine		Meningococcal(Groups A,C,Y,W-135)conjugate vaccine (Menveo) 1 dose plus placebo (0.9% w/v saline for injection) if needed for blinding purposes
Endpoints and definitions	Co-Primary endpoints	Absolute Vaccine efficacy	Time from last study vaccination to the onset of the first occurrence of RT-PCR- or culture-confirmed influenza, due to any influenza Type A or B strain, and regardless of an antigenic match to the strains selected for the seasonal vaccine that occurred more than 14 days after the last vaccination until the end of the influenza season. The primary and co-primary endpoints were met if the lower limit of the 2-sided 95% CI of the absolute vaccine efficacy estimate was greater than 20% (primary endpoint) using protocol definition of ILI in 2 to <18 yrs or greater than 30% (co-primary endpoint) in subjects 3 to <18 yrs of age

	Secondary endpoints	Absolute Vaccine efficacy	Secondary endpoint 1: the time from the last study vaccination to the onset of the first occurrence of either RT-PCR- or culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <9 years, 4 to <18 years, and 9 to <18 years Secondary endpoint 2: the time from the last study vaccination to the onset of the first occurrence of RT- PCR-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years. Secondary endpoint 3: the time from the last study vaccination to the onset of the first occurrence of culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years. Secondary endpoint 4: the time from the last study vaccination to the onset of the first occurrence of culture-confirmed influenza due to influenza Type A or B strain antigenically matched to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years.
Database lock	01 Oct 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) Efficacy - All subjects in the All Enrolled Set who received at least one dose of study vaccine and were evaluated for efficacy from 14 days after the last vaccination, ages 2 to <18 years and 3 to < 18 years of age		

Descriptive statistics and estimate variability	Co-Primary Endpoints	Treatment group	QIVc	Comparator	aVE Point Estimate (95%CI)
		Number of subjects 2 to <18 yr	2257	2252	
		RT-PCR or Culture Confirmed Influenza, any Type Number of Cases (Attack Rate)	175 (7.8)	364 (16.2)	54.63 (45.67,62.12)
			Success criterion met if the lower limit of the 2-sided 95% CI of the absolute vaccine efficacy estimate was greater than 20%		

		Number of subjects 3 to <18 yr	2208	2201	
		RT-PCR or Culture Confirmed Influenza, any Type Number of Cases (Attack Rate)	171 (7.7)	351 (15.9)	54.03 (44.80, 61.71)
			Success criterion met if the lower limit of the 2-sided 95% CI of the absolute vaccine efficacy estimate was greater than 30%		
Effect estimate per comparison		Secondary Endpoint nº1 RT-PCR or Culture Confirmed Influenza, any Type	First occurrence of either RT-PCR- or culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <9 years, 4 to <18 years, and 9 to <18 years		
		Treatment Group	QIVc	Comparator	
		Number of Subjects (age range)	1146 (2 to < 9 yrs)	1142 (2 to < 9 yrs)	
		Number of Cases (Attack Rate)	123 (10.7)	234 (20.5)	
		aVE Point Estimate, 2-9 YoA (95% CI)	50.51 (38.43, 60.22)		
		Number of Subjects (age range)	2045 (4 to <18 yrs)	2032 (4 to <18 yrs)	
		Number of Cases (Attack Rate)	154 (7.5)	310 (15.3)	
		aVE Point Estimate, 4-18 YoA (95% CI)	53.33 (43.38, 61.54)		
		Number of Subjects (age range)	1111 (9 to < 18 yrs)	1110 (9 to < 18 yrs)	
		Number of Cases (Attack Rate)	52 (4.7)	130 (11.7)	
		aVE Point Estimate, 9-<18 YoA (95% CI)	61.85 (47.37, 72.34)		
		Secondary Endpoint nº2 RT-PCR-confirmed, any Type	First occurrence of RT- PCR-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years.		
		Treatment Group	QIVc	Comparator	
		Number of Subjects (age range)	2257 (2 to <18 yrs)	2252 (2 to <18 yrs)	

Number of Cases (Attack Rate)	175 (7.8)	364 (16.2)
aVE Point Estimate 2-<18 YoA (95% CI)	54.63 (45.67,62.12)	
Number of Subjects (age range)	1146 (2 to <9 yrs)	1142 (2 to <9 yrs)
Number of Cases (Attack Rate)	123 (10.7)	234 (20.5)
aVE Point Estimate 2-<9 YoA (95% CI)	50.51 (38.43, 60.22)	
Number of Subjects (age range)	2045 (4 to <18 yrs)	2032 (4 to <18 yrs)
Number of Cases (Attack Rate)	154 (7.5)	310 (15.3)
aVE Point Estimate 4-<18 YoA (95% CI)	53.33 (43.38,61.54)	
Number of Subjects (age range)	1111 (9 to <18 yrs)	1110 (9 to <18 yrs)
Number of Cases (Attack Rate)	52 (4.7)	130 (11.7)
aVE Point Estimate 9-<18 YoA (95% CI)	61.85 (47.37, 72.34)	
Secondary Endpoint nº3 Culture-confirmed influenza, any Type	First occurrence of culture-confirmed influenza due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season in subjects 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years.	
Treatment Group	QIVc	Comparator
Number of Subjects (age range)	2257 (2 to <18 yrs)	2252 (2 to <18 yrs)
Number of Cases (Attack Rate)	115 (5.1)	279 (12.4)
aVE Point Estimate 2-<18 YoA (95% CI)	60.81 (51.30, 68.46)	
Number of Subjects (age range)	1146 (2 to <9 yrs)	1142 (2 to <9 yrs)
Number of Cases (Attack Rate)	79 (6.9)	190 (16.6)
aVE Point Estimate 2-<9 YoA (95% CI)	60.78 (49.01,69.83)	

Number of Subjects (age range)	2045 (4 to <18 yrs)	2032 (4 to <18 yrs)
Number of Cases (Attack Rate)	101 (4.9)	237 (11.7)
aVE Point Estimate 4-<18 YoA (95% CI)	59.66 (49.08,68.05)	
Number of Subjects (age range)	1111 (9 to <18 yrs)	1110 (9 to <18 yrs)
Number of Cases (Attack Rate)	36 (3.2)	89 (8.0)
aVE Point Estimate 9-<18 YoA (95% CI)	60.72 (42.14,73.33)	
Secondary Endpoint nº4 Culture-confirmed influenza, matched	First occurrence of culture-confirmed influenza due to influenza Type A or B strain antigenically matched to the strains selected for the seasonal vaccine, that occurred more than 14 days after the last vaccination until the end of the influenza season 2 to <18 years, 2 to <9 years, 4 to <18 years, and 9 to <18 years.	
Treatment Group	QIVc	Comparator
Number of Subjects (age range)	2257 (2 to <18 yrs)	2252 (2 to <18 yrs)
Number of Cases (Attack Rate)	90 (4.0)	236 (10.5)
aVE Point Estimate 2-<18 YoA (95% CI)	63.64 (53.64,71.48)	
Number of Subjects (age range)	1146 (2 to <9 yrs)	1142 (2 to <9 yrs)
Number of Cases (Attack Rate)	64 (5.6)	164 (14.4)
aVE Point Estimate 2-<9 YoA (95% CI)	63.04 (50.66,72.32)	
Number of Subjects (age range)	2045 (4 to <18 yrs)	2032 (4 to <18 yrs)
Number of Cases (Attack Rate)	81 (4.0)	200 (9.8)
aVE Point Estimate 4-<18 YoA (95% CI)	61.58 (50.25,70.33)	
Number of Subjects (age range)	1111 (9 to <18 yrs)	1110 (9 to <18 yrs)

	Number of Cases (Attack Rate)	26 (2.3)	72 (6.5)
	aVE Point Estimate 9-<18 YoA (95% CI)	64.78 (44.84,77.51)	
Notes	The analysis shows that QIVc prevented RT-PCR- or culture confirmed influenza caused by any Type A or B strain in subjects 2 to < 18 years of age (primary efficacy endpoint) and 3 to < 18 years of age (co-primary endpoint). The VE of QIVc in children 2 to < 18 years of age was 54.6% (95% CI: 45.7 to 62.1). The success criterion was met as the LL of the 2-sided 95% CI was above 20%. The VE of QIVc in children 3 to < 18 years of age was 54.03% (95% CI: 44.8 to 61.7). The success criterion was met as the LL of 95% CI for VE is above 30%.		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

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

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

Regarding the blinding, a double blinding it is the preferred strategy, but observer blind can be considered acceptable with no overestimation treatment effects expected.

The statistical methods are considered adequate.

The total number of participants in this study, as well as the stratification by age is considered appropriate to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 20% for the primary endpoint assessment, with approximately 90% power. The Inclusion/Exclusion criteria are considered satisfactory. Moreover, the strains 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.

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

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

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

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. Moreover, it is noted that there are two co-primary endpoints, the first one is that the efficacy of the QIVc would be demonstrated if the lower limit (LL) of the 2-sided 95% confidence interval (CI) for VE is 20%, and for meeting the second one the LL of the 95% CI for vaccine Efficacy (VE) is above 30%. These two figures are sensible.

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, or rhinorrhoea. This ILI definition goes along with the guideline on Influenza vaccines (EMA/CHMP/VWP/457259/2014) recommendations and take into account the European Centre for Disease Prevention and Control (ECDC) definitions for ILI. The Influenza case definition was also properly defined following also de EU recommendations.

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 also analysed. This is considered important to show the overall potential benefit of the vaccine.

The following comment is made in relation to the overall design of the trial. The guideline on Influenza vaccines (EMA/CHMP/VWP/457259/2014) specifically requires a demonstration of vaccine efficacy in the 6-36 month group, for an indication that includes children of this age. For children older than 36 months, the Guideline states: "For an indication for use in children aged from 3 years up to approximately 9 years, in whom the proportion that is primed is likely to be very variable in different settings, authorisation should usually be based on demonstrating that the immune responses to the selected dose and regimen are at least as good as those observed in children aged 6-36 months in whom efficacy has been satisfactorily demonstrated." For this age group (3 to 9 YOA) it also states: "In cases where vaccine efficacy could not be demonstrated in the 6-36 month-olds, the possible basis for an authorisation for use in 3-9 year-olds should be discussed with competent regulatory authorities." In line with this recommendation, the MAH discussed the design of V130_12 study in a follow-up scientific advice in 2016 (EMEA/H/SA/2628/2/FU/1/2016/PED/II) and the CHMP agreed that this study was carried out to demonstrate clinical efficacy in children older than 3 years of age. Originally study V130_12 was designed to be performed in children 4 to 18 YOA, but in a protocol amendment the lower age was changed to 2 YOA. Therefore, the MAH has submitted clinical efficacy data in the whole 2 to <18 age group, which is acknowledged and welcomed, and in accordance with CHMP scientific advice.

As discussed below the results for the 2 to 18 years group clearly support the indication for this age group.

No other measurements now cited in EMA/CHMP/VWP/457259/2014 (for example, single radial haemolysis, cell-mediated immunity, antigen-specific T-cell frequencies, CD4+ and CD8+ responses, activation of memory B cells, or evaluation of anti-neuraminidase antibodies) were assessed in the V130_12 protocol. This cell-mediated immunity will be measured in the ongoing study V130_10, which is a phase III, non-inferior immunogenicity and safety versus licensed QIV comparator in children 6 months to < 4 years of age.

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

Efficacy data and additional analyses

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

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

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

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

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

Table 14: Absolute Vaccine Efficacy (95% CI) for Overall RT-PCR-Confirmed or Culture Confirmed Influenza, and by cultured confirmed matched/unmatched strains in different age strata - FAS Efficacy

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

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

Table 15: Absolute Vaccine Efficacy (95% CI) for Overall RT-PCR-Confirmed or Culture Confirmed Influenza, and per strain based on the vaccination status - FAS Efficacy

VE (95%CI)	Overall RT-PCR or culture confirmed	Type A/H1N1	Type A/H3N2	Type B
Previously vaccinated	58.67 (47.45,67.50)	86.8 (72.34, 93.70)	42.65 (13.5, 61.97)	51.90 (31.25, 66.35)
Not previously vaccinated	48.39 (32.13, 60.75)	73.23 (50.50, 85.52)	41.30 (2.61,64.61)	40.97 (10.62, 61.01)

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

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

The MAH explained that despite the relatively small number of study participants aged 2 to <3 years (100 subjects: 49 in the QIVc group and 51 in the comparator group), the incidence of any RT-PCR- or culture-confirmed influenza, reported during the study period, was high: 13/51 subjects (25.5%) in the comparator group, and 4/49 subjects (8.2%) in the QIVc group (see table 15). The MAH also highlighted that the estimate of vaccine efficacy in children in the 2 to <3 years of age group was 67.97 (95% CI: 8.00, 88.79) and was consistent with efficacy estimates in other age groups, and in the overall study population. In addition, the MAH mentioned that the efficacy of QIVc in "previously vaccinated" and "not previously vaccinated" children was comparable and that there was no difference in strain-specific efficacy against the different influenza strains between these two groups of influenza vaccinated subjects. This point is considered important, since the youngest children are mostly influenza-naïve and it is a potential concern that they do not respond to influenza vaccines as well as older children.

Table 16: Number of subjects with first-occurrence of laboratory-confirmed influenza and absolute vaccine efficacy (95% CI) by any strain and age – Full Analysis set efficacy.

Age	Any Strain - Number of cases (n), Number of Subjects (N), (attack rate)		VE[1] (95% CI)
	QIVc n , N (%)	Comparator n, N (%)	
2 to < 3	4, 49 (8.2)	13, 51 (25.5)	67.97 (8.00, 88.79)
3 to < 6	57, 532 (10.7)	103, 513 (20.1)	46.64 (27.97, 60.47)
6 to < 9	62, 565 (11)	118, 578 (20.4)	46.25 (28.54, 59.57)
9 to < 18	52, 1111 (4.7)	130, 1110 (11.7)	60.04 (45.48, 70.71)
2 to < 18	175, 2257 (7.8)	364, 2252 (16.2)	52.03 (43.11, 59.55)

[1]Unadjusted Vaccine Efficacy (VE) = (1- attack rate of QIVc/ attack rate of comparator) × 100%.

All the data and analysis are considered adequate.

Immunogenicity data

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

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

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

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

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

The vaccine strain composition changed between seasons. Except for the Type A/H1N1 vaccine strain, all other vaccine strains (Type A/H3N2, Type B/Yamagata and Type B/Victoria) were updated for each season. Therefore, all the immunogenicity results were presented by season, even in the case where the strain did not change (e.g. A/H1N1). The FAS Immunogenicity was predominantly White (99.0%), which is a markedly higher proportion than in the All Enrolled Set. The MAH explained that this was due to the geographical location of these subjects (Estonia, Finland, Poland, and Lithuania) limited by enrolment in Seasons 2 and 3. Four subjects were of Hispanic or Latino origin, all other subjects were of "Not Hispanic or Latino" origin. It would have been optimal to include participants from different ethnic groups, however

having in mind all the scientific knowledge on the immune response to influenza vaccines in different races, it is not expected that this issue introduces any bias.

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

Assessment of paediatric data on clinical efficacy

This addendum provides information on the clinical study completed for QIVc, Study V130_12 (NCT03165617), a Phase 3/4 efficacy, immunogenicity and safety study in children 2 to < 18 years of age. This study was a regulatory (post-marketing) requirement to confirm the clinical benefit of QIVc for use in children ≥4 years of age in the US consistent with regulations for accelerated approval (US Code of Federal Regulations 21 CFR 601.40-46). To fulfil additional registration requirements with the European Union (EU) children ≥2 years of age were also enrolled in this study to further evaluate QIVc in a broader age range.

The V130_12 QIVc trial was appropriately designed and all the efficacy primary and co-primary endpoints were met. Moreover, this trial is part of the PIP and has been discussed with the PDCO.

2.4.4. Conclusions on the clinical efficacy

In the initial MAA, the indication sought by the MAH was the prevention of influenza in children 4 years of age and older and adults. The data to support the adult indication (older than 18 YOA) were found to be sufficient by the CHMP. Nevertheless, the indication finally granted for children only covered the age between 9 and 18 years of age.

With the current application, the MAH is submitting the data from the efficacy study V130_12, in support of an extension of the indication from 2 years of age and above.

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

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

In regard to the assessments of immunogenicity, study V130_12 has generally followed the EU Guideline on Influenza Vaccines Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014) and the CBER Guidance for the Licensure of Seasonal Influenza Vaccines (CBER, 2007). Also, the design of this study has been discussed with EMA through several scientific advices and the CHMP advice has been followed. As recommended, the assessment of vaccine efficacy used laboratory-confirmed influenza as the primary endpoint, and in a subset of subjects, immunogenicity was assessed via the haemagglutinin inhibition (HI) and microneuralization (MN) assays. Serology was assessed at baseline (i.e., before vaccination) and at 3 weeks after the last vaccination, which is approximately when the HI antibodies reach their peak in human sera (Kunzel et al., 1996). In conclusion, there was a robust and substantial immune response

across the 2 seasons in subjects who received QIVc; even with seasonal differences in vaccine strains and baseline GMTs.

Regarding the demonstration of efficacy for each paediatric age group, the requirements of the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014) are:

- The guideline specifically requires a demonstration of vaccine efficacy in the 6-36 month group, for an indication that includes children of this age.
- For an indication for use in children aged from 3 years up to approximately 9 years, in whom the proportion that is primed is likely to be very variable in different settings, authorisation should usually be based on demonstrating that the immune responses to the selected dose and regimen are at least as good as those observed in children aged 6-36 months in whom efficacy has been satisfactorily demonstrated. In cases where vaccine efficacy could not be demonstrated in the 6-36 month olds, the possible basis for an authorisation for use in 3-9 year-olds should be discussed with competent regulatory authorities.
- For an indication that includes use from approximately 9 years to < 18 years, a demonstration of vaccine efficacy is not required. Authorisation may be based on a direct comparison of immune responses to the candidate vaccine between subjects aged 9-<18 years and young adults or directly against an authorised inactivated non-adjuvanted seasonal influenza vaccine administered to the same age group.

In the case of the V130_12 study, the MAH discussed the trial design with EU regulatory authorities through the scientific advice procedure, and the CHMP agreed with the MAH's proposal to carry out an absolute efficacy study in children 3 years of age and older.

As it is detailed in section on "Demographic and Baseline data", 50.7% of the subjects were in the age strata 2 to<9 YOA, so the high aVE obtained in this age subgroup supports the requested indication for this age subgroup. Moreover, in the youngest age subgroup (2 to < 4 YOA) aVE was 62.66 (95%CI : 38.06 -,77.49). However, it was noted that the number of subjects included in this age strata were 332 subjects, but that only 100 (49 received QIVc and 51 the comparator vaccine) of them were in the age strata 2 to <3 YOA. Considering that the CHMP guideline on Influenza vaccines (EMA/CHMP/VWP/457259/2014) clearly states that a demonstration of vaccine efficacy is required for an indication that includes use in children from 6 to 36 months, stratified 24 to <36 months of age data were requested. The MAH provided a justification regarding the results obtained in this very small group (49 subjects 24-36 months of age) and highlighted why they are relevant to support an indication for this age strata. Despite the relatively small number of study participants aged 2 to <3 years, the incidence of any RT-PCR- or culture-confirmed influenza, reported during the study period, was high: 13/51 subjects (25.5%) in the comparator group, and 4/49 subjects (8.2%) in the QIVc group. The MAH also emphasized that the estimate of vaccine efficacy in children in the 2 to <3 years of age group was 67.97 (95% CI: 8.00, 88.79) and was consistent with efficacy estimates in other age groups, and in the overall study population. In addition, the MAH mentioned that the efficacy of QIVc in "previously vaccinated" and "not previously vaccinated" children was comparable and that there was no difference in strain-specific efficacy against the different influenza strains between these two groups of influenza vaccinated subjects. This point is considered important, since the youngest children are mostly influenza-naïve and it is a potential concern that they do not respond to influenza vaccines as well as older children. In conclusion, it is agreed with the Company that the study results indicate a consistent performance of QIVc vaccine in children 2 through 18 years of age, including subjects 2 to <3 years of age.

In conclusion, the data provided by the MAH support the indication for prophylaxis of influenza in subjects of 2 years of age and older.

2.5. Clinical safety

Introduction

The current indication for Flucelvax Tetra is established for children aged 9 years and older, adolescents and adults. The safety profile of Flucelvax Tetra was based on the data from 2 clinical studies comparing QIVc to TIVc. Both studies (study V130_01 and study V130_03) were phase 3 trials conducted in the US, in adults 18 years of age and above (including elderly adults), and in subjects 4 to < 18 years of age, respectively. Therefore, the QIVc database accounted was of 1324 subjects ≥ 18 years of age and 1159 subjects 4 to <18 years. Additionally this database was supported by the safety data set coming from the TIVc studies.

The most common adverse reactions reported in adults ≥18 years of age were injection site pain, headache, fatigue, followed by erythema and myalgia. In the paediatric population, the most common adverse reactions reported were pain, tenderness and erythema followed by headache, fatigue and myalgia. The majority of solicited reactions were mild to moderate in severity in all age groups studied.

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

Patient exposure

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

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

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

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

Adverse events

Solicited Adverse Events

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

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

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

Table 17: Number (%) of subjects 2 to < 18 Years of Age with at least one solicited adverse event 30 minutes postvaccination and/or day 1 (6 hours) through 7 days after any vaccination – solicited safety set

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

* Solicited safety population. 3 subjects did not return their diary card so they were excluded from the exposed population of 2258.

Solicited Local Adverse Events

The percentage of subjects with any solicited local AE reported from Day 1 (6 hours) through Day 7 after vaccination was 36.8% in the QIVc group and 33.6% in the comparator group (see table 16). No notable differences in the rate of solicited local AEs were observed between the QIVc and the comparator, except for a slightly higher rate of pain in the QIVc (23.8% in QIV group *vs* 19.0% in comparator group), but a slightly lower rate of induration and erythema observed in the QIVc group vs the comparator. The most commonly reported solicited local AEs were tenderness, pain and erythema; the majority were mild to moderate in severity (the proportion of subjects with severe local AEs in OIVc groups was ≤1%). See table 17.

Table 18: Number (%) of subjects 2 to < 18 Years of Age with solicited local adverse event from 6 hours through 7 days after any vaccination – solicited safety set

Solicited Local Adverse Event	QIVc N=2255 n (%)	Comparator N=2254 n (%)
Induration (mm)	N=2246	N=2239
Any	286 (12.7)	294 (13.1)
Severe[a]	3 (0.1)	7 (0.3)
Erythema (mm)	N=2246	N=2242
Any	433 (19.3)	476 (21.2)
Severe[a]	4 (0.2)	17 (0.8)
Ecchymosis (mm)	N=2244	N=2240
Any	169 (7.5)	142 (6.3)
Severe[a]	0 (<0.1)	1 (<0.1)
Pain[b]	N=1658	N=1679
Any	395 (23.8)	319 (19.0)
Severe	12 (0.7)	20 (1.2)
Tenderness[b]	N=578	N=562
Any	166 (28.7)	143 (25.4)
Severe	6 (1.0)	8 (1.4)

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

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

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

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

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

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

Solicited Systemic Adverse Events

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

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

Table 19: Number (%) of subjects 2 to < 18 Years of Age with solicited systemic adverse events from 6 hours through 7 days after any vaccination – solicited safety set

Solicited Systemic Adverse Event	QIVc N=2255 n (%)	Comparator N=2254 n (%)
Loss of appetite[a]	N=1674	N=1685
Any	154 (9.2)	129 (7.7)
Severe	8 (0.5)	9 (0.5)
Nausea (feeling the need to vomit)[a]	N=1668	N=1684
Any	95 (5.7)	93 (5.5)
Severe	2 (0.1)	11 (0.7)
Muscle aches all over the body[a]	N=1668	N=1683
Any	84 (5.0)	84 (5.0)
Severe	7 (0.4)	8 (0.5)
Aching in several joints[a]	N=1669	N=1682
Any	108 (6.5)	129 (7.7)
Severe	6 (0.4)	8 (0.5)
Headache[a]	N=1668	N=1685
Any	278 (16.7)	261 (15.5)
Severe	17 (1.0)	10 (0.6)
Feeling fatigue or tiredness[a]	N=1669	N=1684
Any	265 (15.9)	274 (16.3)
Severe	17 (1.0)	17 (1.0)
Shivering/chills[b]	N=2249	N=2248
Any	145 (6.5)	128 (5.7)
Severe	11 (0.5)	7 (0.3)
Loose stools or diarrhea	N=2249	N=2250
Any	156 (6.9)	168 (7.5)
Severe	10 (0.4)	10 (0.4)
Vomiting or throwing up	N=2250	N=2248
Any	89 (4.0)	80 (3.6)
Severe	10 (0.4)	11 (0.5)
Change in eating habits[c]	N=578	N=564
Any	57 (9.9)	57 (10.1)
Severe	6 (1.0)	4 (0.7)
Sleepiness[c]	N=578	N=564
Any	86 (14.9)	99 (17.6)
Severe	5 (0.9)	10 (1.8)
Irritability[c]	N=578	N=564
Any	80 (13.8)	61 (10.8)
Severe	1 (0.2)	3 (0.5)
Fever	N=2247	N=2242
Any (>=38.0°C)	118 (5.3)	102 (4.5)
>=40.0°C	7 (0.3)	5 (0.2)

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

Abbreviations: Men ACWY = meningococcal (Serogroup ACWY) conjugate vaccine; QIVc = cell derived quadrivalent subunit influenza virus vaccine.

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

Unsolicited Adverse Events

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

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

Table 20: Overall summary of reportable treatment-emergent unsolicited adverse events in subjects 2 to < 18 Years of Age – As treated - Overall safety set

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

Source: Section 5.3.5.1, CSR V130_12 Table 12-3

Abbreviations: AE = adverse event; Men ACWY = meningococcal (Serogroup ACWY) conjugate vaccine; NOCD = new onset chronic disease; QIVc = cell derived quadrivalent subunit influenza virus vaccine; SAE = serious adverse event.

[a] Day 22 for all "previously vaccinated" subjects (receiving a single vaccine dose) and Day 50 for all "not previously vaccinated" subjects (receiving 2 doses).

[b] Medically-attended AEs were collected through the first 30 days after the first occurrence of influenza-like illness.

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

Note 2: Related AEs include AEs that were considered as at least possibly related to study vaccination.

Note 3: Severity is based on the greatest severity associated with a preferred term for a reported AE.

The number (%) of subjects 2 to < 18 years of age who reported unsolicited AEs that were considered to be at least possibly related to the study vaccination, observed in >1% in QIVc group, were Influenza like

illness (1.1%). Other unsolicited AEs considered as related to the study vaccine were reported as less than 0.7% (Upper respiratory tract infection, rhinitis, rhinorrhoea, cough and nasopharyngitis)

Serious adverse event/deaths/other significant events

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

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

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

No AEs leading to withdrawal from the study were reported.

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

Safety in special populations

Intrinsic Factors

By Age

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

Solicited AEs:

In the analysis by age subgroups, the proportion of subjects with any solicited local AEs within 30 minutes after any vaccination were low for the QIVc (0.4%-1.4%) and the comparator group (0.7% - 1.4%) in all age subgroups. The most commonly reported local solicited AEs after 7 day following any vaccination for both vaccine groups were tenderness (in the 2 to <6 years aged group), pain (in the 6 to <9 years aged group and in 9 to <18 years aged group) and erythema in all age groups. Additionally, the older children (9 to <18 years of age) reported overall a slightly lower percentage of solicited AEs compared to the younger children (including pain).

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

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

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

Additionally, the older children (9 to <18 years of age) reported overall a slightly lower percentage of solicited AEs compared to the younger children.

The most common (≥10%) local and systemic adverse reactions after any vaccination in children 6 to less than 9 years of age were pain at the injection site (61%), injection site erythema (25%), injection site induration (19%), fatigue (16%), headache (16%) and injection site ecchymosis (11%).

The most common (≥10%) local and systemic adverse reactions after any vaccination in children 2 to less than 6 years of age were tenderness at the injection site (54%), injection site erythema (23%), sleepiness (21%), irritability (19%), injection site induration (15%), change in eating habits (14%) and injection site ecchymosis (11%).

Unsolicited AEs:

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

By gender

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

By racial/ethnic origin

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

Extrinsic Factor

By vaccination status

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

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

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

Post marketing experience

QIVc was approved in the US for prevention of influenza in persons 4 years of age and older on 23 May 2016. Safety data in adults and children from 9 years of age onwards have been provided in UE since its approval on 12th December 2018. The same vaccine was approved in Canada on 22 November 2019 for subjects 9 years of age and older, and in Brazil for people aged 18 years and older since February 2020.

Additional adverse events were reported from postmarketing surveillance, as summarized in the most recent QIVc Periodic Safety Update Report. Post marketing experience with QIVC has not identified any safety concern. There was no change to the safety information during the report in the period and the cumulative experience reminded in accordance with the RMP.

2.5.1. Discussion on clinical safety

The current indication for Flucelvax Tetra is established for children aged 9 years and older, adolescents and adults. This indication was based on the data provided by 2 clinical studies comparing QIVc to TIVc: Study V130_01 in subjects 2 to <18 years of age, and study V130_03, in subjects 4 to < 18 years of age.

An additional clinical study Phase 3/4 (V130_12) has been provided to support the authorisation of Seqirus' cell-based quadrivalent influenza vaccine (QIVc) for the prevention of influenza in adults and children from 2 years of age onwards. In V130_12, Flucelvax tetra was compared to a non-influenza comparator (Menveo) in children of 2 to <18 years of age. Co-administration of other vaccines was not investigated in this study.

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

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

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

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

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

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

percentage of solicited local and systemic AEs within the 30 minutes after vaccination compared to the younger children.

The solicited AEs (local and systemic) rates from 6 hours through Day 7 after any vaccination, stratified by the different age subgroups (2 to <6, 6 to <9 and 9 to <18), to establish comparisons in terms of reactogenicity between the study vaccine and the comparator in the different age groups were provided. Overall, no notable differences in the rate of solicited local and systemic AEs were observed between the QIVc and the comparator in any age subgroup. Only, a slightly higher rate of tenderness in the QIVc in 2 to <6 yoa subjects and a slightly higher rate of pain, chills, headache and body temperature ≥38.0ºC in the QIVc group in 6 to <9 yoa group was reported. The majority of the reported solicited local and systemic AEs in any age group were mild to moderate in severity. Additionally, the older children (9 to <18 years of age) reported overall a slightly lower percentage of solicited AEs compared to the younger children.

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

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

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

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

2.5.2. Conclusions on clinical safety

After assessing the submitted safety data collected in the new phase III study V130_12, the QIVc safety profile is in general comparable to that of the non-influenza comparator vaccine. No new safety signal has been observed in the submitted clinical database. It can be concluded that QIVc vaccine in subjects 2 to <9 years of age does not have any clinically relevant safety issue.

Therefore, the safety profile of QIV is considered to be adequate to support the indication for prophylaxis of influenza in subjects of 2 years of age and older.

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/was requested to submit an updated RMP version with this application.

The PRAC considered that the risk management plan version 2.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Safety in immunocompromised patients
	Safety in subjects with underlying diseases
	Use in pregnant and breastfeeding women

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 – Required additional pharmacovigilance activities				
Pregnancy Registry – V130_110B	Evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunized as part of routine care with the seasonal cell culture influenza TIVc or QIVc vaccine during pregnancy.	Major congenital malformations in new-borns, preterm birth and low birth weight outcomes	Final report	31 December 2021
Additional pharmacovigilance activities not required by regulators				
A non-interventional study of vaccine effectiveness; QIVc versus no vaccination (DRIVE sub-analysis).	To perform an analysis of influenza vaccine effectiveness of QIVc vaccination versus no vaccination in persons of an age aligned with the applicable age indication.	None	Annual reports	First annual report by 31 December 2020 and annually thereafter.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks: None		
Important potential risks: None		
Missing information		
Safety in immunocompromised patients	Routine risk minimisation measures: SmPC section 4.4 PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Safety in subjects with underlying diseases	Routine risk minimisation measures: SmPC section 4.4. PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
Use in pregnant/breastfeeding women	Routine risk minimisation measures: SmPC section 4.6 PL Section 2 Additional risk minimisation measures: None	Required additional pharmacovigilance activities for the FDA BLA 125408/127: A Pregnancy Registry (V130_110B) to evaluate pregnancy outcomes as well as events of interest of major congenital malformations, preterm birth and low birth weight among women immunized as part of routine care with the seasonal cell culture quadrivalent (QIVc) vaccine during pregnancy is ongoing.

2.7. Update of the Product information

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

Immunogenicity information, GMT and seroconversation rates, for study V130_03 has been updated in section 5.1 of the SmPC in order to include the patients from 4YoA who were excluded, as these were not originally covered in the indication.

2.7.1. User consultation

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

2.7.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

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

3.1.2. Available therapies

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

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

For many years, seasonal influenza vaccines included antigens from 3 influenza strains in their composition, 2 influenza A strains (largely A/H1N1 and A/H3N2), and a strain from 1 of the 2 influenza B lineages (B/Yamagata or B/Victoria). However, TIVs have been associated with potential for vaccine mismatch depending on whether B/Yamagata or B/Victoria is chosen for inclusion in the seasonal vaccine. Indeed, the predicted B strain included in the recommended northern hemisphere seasonal influenza vaccine was incorrect during 5 of 10 influenza seasons from 2001/2002 to 2010/2011. In order to avoid vaccine mismatch, quadrivalent influenza vaccines that include influenza B strains from both lineages have been recommended and these are expected to provide protection against the additional B strain.

Flucelvax Tetra is intended for prophylaxis of influenza in adults and children from 9 years of age and should be used in accordance with official recommendations. Flucelvax Tetra is a quadrivalent inactivated

influenza vaccine including B strains of both lineages and is therefore expected to improve protection in target populations, especially in children where significant disease due to influenza B strains occurs and the potential for vaccine B strain mismatch has existed with trivalent influenza virus vaccines. Other quadrivalent influenza vaccines are authorised for use in adults and children both at the national and at the centralised level in Europe; as such there is not an unmet medical need. However, it is important to have different options available on the market. In addition, this vaccine is prepared in cell culture differently to others, which may constitute an alternative for people allergic to eggs. A need exists in younger children (i.e. <4YOA), such as those not already naturally primed by influenza virus.

3.1.3. Main clinical studies

At the time of marketing authorisation, the clinical development program of QIVc included two-phase III stratified, randomized, double-blind, multicentre studies that were conducted to evaluate the safety and efficacy (immunogenicity) of the QIVc in children and 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 randomized 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.

The scope of this variation is to extend the indication to 2 years of age and above. For that aim, the MAH presents the results from study V130_12, a phase 3/4 efficacy, immunogenicity and safety study in children 2 to < 18 years of age.

3.2. Favourable effects

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

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

The primary and co-primary efficacy endpoints, absolute vaccine efficacy (aVE) relative to comparator against any influenza Type A or B strain were achieved. The analysis showed that QIVc prevented RT-PCR- or culture-confirmed influenza caused by any Type A or B strain in subjects 2 to < 18 years of age (primary efficacy endpoint) and 3 to < 18 years of age (co-primary endpoint). The VE of QIVc in children 2 to < 18 years of age was 54.6% (95% CI: 45.7 to 62.1). Success criterion were met as the LL of the 2-sided 95% CI was above 20%. The VE of QIVc in children 3 to < 18 years of age was 54.0% (95% CI: 44.8 to 61.7). The success criterion was met as the LL of 2-sided 95% CI for VE is above 30%. Moreover, the secondary efficacy objectives that were efficacy against RT-PCR or culture-confirmed influenza in the overall study population 2 to < 18 years of age either due to any influenza type A or B strain or due to influenza type A or B antigenically matched strains were also met. The VE numbers were 54.63% (95% CI [45.67, 62.12]) for PCR-confirmed regardless of antigenic match, 60.81% (95% CI [51.30, 68.46]) for

cultured-confirmed regardless of antigenic match, and 63.64% (95% CI [53.64; 71.48]) for culture-confirmed and matched to the strains contained in the vaccine.

The VE was also analysed in several age cohorts, with similar results to those obtained in the overall study.

All the data and analysis are considered adequate, and robust to support the indication for prevention of influenza in adults and children from 2 years 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.) which 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.

Concomitant administration with other vaccines was not assessed, particularly those recommended in the childhood immunization programs.

3.4. Unfavourable effects

In the initial MAA of Flucelvax Tetra, data were presented from study V130_03. In this study, a total of 2333 subjects 4 to < 18 years of age were enrolled, including 1161 in the 4 to < 9 years age group and 1171 in the 9 to <18 years age group. The solicited safety set included 1135 subjects exposed to QIVc, 570 to TIV1c, and 563 to TIV2c, while the unsolicited safety set included 1149 subjects exposed to QIVc, 579 to TIV1c, and 570 to TIV2c.

The rates of reported solicited local and systemic AEs in study V130_03 were generally similar to those reported in study V130_12, which is the scope of this variation. Nevertheless, some differences were observed, especially in the solicited local AEs, in which less events were reported in study V130_12 than in the previous V130_03 study.

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

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

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

moderate in severity. Fever (≥38°C) was reported by 5.3% and 4.5% in QIVc and comparator group, respectively.

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

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

3.5. Uncertainties and limitations about unfavourable effects

It appears that ethnical differences have a small impact on the rates of solicited AEs. In fact, comparing the rates reported by any solicited AEs in the new V130_12 study in subjects 2 to < 18 years of age with the study V130_03 performed in 4 to <18 years of age group, the data observed in the QIVc group were lower in the new study (51.4% and 72% respectively). Approximately 50% of enrolled subjects in study V130_12 were Asian, and another 50% were White (Table 10-6 of the V130_12 CSR). In study V130_03, the majority of enrolled subjects were White, with <1% (9 children) of Asian origin. After stratification by ethnic origin it is observed that the lower rate of solicited local AEs in study V130_12 was substantially driven by the results observed in the Asian population since the rates of each solicited local AE appeared to be lower in Asian subjects compared to White subjects. The MAH states that a difference in the reporting rates of solicited local AEs in Asian versus White paediatric subjects has also been observed in other studies conducted by Seqirus. The effect observed does not alter the B/R assessment of this vaccine.

3.6. Effects Table

Table 21. Effects Table for Flucelvax tetra for the extension of indication of prophylaxis of influenza to children from 2 years of age.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Absolute Vaccine Efficacy: overall Subjects 2 to <18 YOA	QIVc Vaccine, n=2257 Comparator, n=2252	% (95% CI)	54.63 (45.67, 62.12) Cases = 175	Cases = 364	Co-Primary endpoint	Study V130_12
aVE overall Subjects 3 to <18 YOA	QIVc Vaccine, n=2208 Comparator, n=2201	% (95% CI)	54.03 (44.80, 61.71) Cases = 171	Cases = 351	Co-Primary endpoint	Study V130_12
Unfavourable Effects						
Solicited local AEs Subjects 2 to <18 YOA	QIVc Vaccine, n=2257 Comparator, n=2252	Incident rate (%)	36.9 33.6		Secondary safety endpoint	Study V130_12
Solicited systemic AEs Subjects 2 to	QIVc Vaccine, n=2257	Incident rate (%)	31.4		Secondary safety endpoint	Study V130_12

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
<18 YOA	Comparator, n=2252		30.5			

Abbreviations: aVE: absolute vaccine efficacy, QIVc: Flucelvax Tetra, quadrivalent influenza vaccine grown in cell culture, YOA: years of age, CI: confidence interval.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

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

In terms of safety, the safety profile for Flucelvax Tetra in children 2 to 18 years of age is in general comparable to that of the non-influenza comparator vaccine. No new safety signal has been observed in the submitted clinical database. It can be concluded that QIVc vaccine in subjects 2 to <9 years of age does not raise any relevant safety issue.

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 2 years of age and above.

3.8. Conclusions

The overall B/R of Flucelvax Tetra in children 2 to 18 years is considered 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 and IIIB

Extension of the indication of prophylaxis of influenza, from the currently approved age range "adults and children from 9 years of age" to "adults and children from 2 years of age" for Flucelvax Tetra; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been approved.

The variation leads to amendments to the Summary of Product Characteristics 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 Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0084/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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 “Flucelvax Tetra EMEA/H/C/004814/II/0013”