EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2020
EMA/200444/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fluad Tetra

Common name: influenza vaccine (surface antigen, inactivated, adjuvanted)

Procedure No. EMEA/H/C/004993/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

AE	Adverse Event
AEFI	Adverse Events Following Immunization
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
Anti-NA	Anti-Neuraminidase
aQIV	Adjuvanted Quadrivalent Influenza Vaccine
AS	Active Substance
AST	Aspartate Aminotransferase
aTIV	Adjuvanted Trivalent Influenza Vaccine
AUC	Area Under the Curve
BMI	Body Mass Index
BPC	Bio Process Containers
B/R	Benefit – Risk
BSE	Bovine Spongiform Encephalopathy
CBER	Center for Biologics Evaluation and Research
CDC	Center of Disease Control and Prevention
CDP	Clinical Development Plan
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMI	Cell Mediated Immunity
CoA	Certificate of Analysis
CoP	Correlate of Protection
COPD	Chronic Obstructive Pulmonary Disease
CPP	Critical Process Parameter
CRF	Case Report Form
CSR	Clinical Study Report
CT	Clinical Trial
CTAB	CetylTrimethyl-Ammonium Bromide
CTD	Common Technical Document
DMC	Data Monitoring Committee
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
ELISA	Enzyme-Linked ImmunoSorbent Assay
ELLA	Enzyme-Linked Lectin Assay
EMA	European Medicines Agency
ER	Event Rate
ERA	Ecotoxicity/environmental Risk Assessment
EU	European Union
EURD	European Union Reference Dates
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FP	Finished Product
FSFV	First Subject, First Visit
FTT	Failure To Thrive
GCP	Good Clinical Practice
GL	Guideline
GLM	General Linear Model
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

GMT	Geometric Mean Titre
GMTr	Geometric Mean Titre Ratio
GMR	Geometric Mean Ratio
HA	Haemagglutinin
HI	Haemagglutination inhibition
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HSV	Herpes Simplex Virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Reports
ID	Idenfication
IIV	Inactivated Influenza Vaccines
ILI	Influenza-Like Illness
IM	IntraMuscular
IRT	Interactive Response Technology
IPC	In-Process Control
IV	IntraVenous
KPP	Key Performance Parameter
LL	Lower Limit
LoOI	List of Outstanding Issues
LoQ	List of Questions
LSLV	Last Subject, Last Visit
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MCAR	Missing Completely at Random
Mcg	Microgram(s)
MDCK	Madin-Darby Canine Kidney
MedDRA	Medical Dictionary for Regulatory Activities
MFAS	Modified Full Analysis Set
MF59	MF59C.1 adjuvant
MN	MicroNeutralization
MOPA	Multiplex Opsonophagocytic killing Assay
MPH	Monovalent Pooled Harvest
MS	Master Seed
NA	Neuraminidase
NAS	New Active Substance
ND	Not Determined
NH	North Hemisphere
NOCD	New Onset Chronic Diseases
NP	NasoPharyngeal
OI	Opsonic Index
OPA	Opsonophagocytic Activity
PACMP	Post-Approval Change Management Protocol
PBS	Phosphate-Buffered Saline
PCV13	13-valent Pneumococcal Conjugate Vaccine
Ph. Eur.	European Pharmacopoeia
PO	Oral
PPQ	Process Performance Qualification

PPS	Per Protocol Set
PPSV23	23-valent Pneumococcal Polysaccharide Vaccine
PRAC	Pharmacovigilance Risk Assessment Committee
PRR	Proportional Reporting Rate
PSUR	Periodic Safety Update Report
PT	Preferred Term
QA	Quality Attribute
QIV	Quadrivalent Influenza Vaccine
REC	Recommendation
RMP	Risk Management Plan
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
rVE	Relative Vaccine Efficacy
SA	Scientific Advice
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Seroconversion
SCR	Seroconversion Rate
SD	Standard Deviation
SDR	Signal of Disproportionate Reporting
SDS-PAGE	Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis
SH	South Hemisphere
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SMS	Short Message Service
SOC	System Organ Class
SPF	Specified-Pathogen-Free
SRID	Single Radial Immunodiffusion
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIV	Trivalent Influenza Vaccine
TNF-α	Tumor Necrosis Factor α
TSE	Transmissible Spongiform Encephalopathies
UK	United Kingdom
UL	Upper Limit
US, USA	United States of America
USP	United States Pharmacopeia
VE	Vaccine Efficacy
VWP	Vaccines Working Party
WBC	White Blood Cell
WFI	Water For Injection
WHO	World Health Organization
WS	Working Seed

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Seqirus Netherlands B.V. submitted on 5 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Fluad Tetra, through the centralised procedure under Article 28 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 February 2018.

The applicant applied for the following indication

"*Active immunisation against influenza in the elderly (65 years of age and older).*

Active immunisation against influenza in children 6 months to less than 6 years of age.

[invented name] should be used in accordance with official recommendations"

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0057/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0057/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance influenza vaccine (surface antigen, inactivated, adjuvanted) contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

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
24 October 2013	EMEA/H/SA/2577/1/2013/PED/III	Dr Jan Mueller-Berghaus and Dr Hans Ovelgönne
23 June 2016	EMEA/H/SA/2577/2/2016/III	Dr Jens Reinhardt and Dr Hans Ovelgönne

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

The advice provided during the procedure EMEA/H/SA/2577/1/2013/PED/III regarding the paediatric indication development. The advice pertained to the following aspects:

- Harmonization of Release Specification and Potency Testing strategy for determining HA content for commercial aQIV;
- Use of US Release criteria and Parallel Line method for phase 3 Trial;
- The aQIV clinical development plan leveraging prior data with the aTIV (Fluad) in children 6 months to <72 months of age;
- The design of the pivotal safety efficacy and immunogenicity study in children 6-<72m including a subgroup of children in high risk of influenza complications;
- The plan not to conduct a lot to lot consistency study for aQIV.

The advice provided during the procedure EMEA/H/SA/2577/2/2016/III regarding the elderly indication development. The advice pertained to the following aspects:

- The non-clinical and clinical data package for licensure of aQIV in $\geqslant$ 65 years old leveraging prior data with aTIV (Fluad) considering that:
    - aQIV and aTIV (Fluad) are manufactured using the same manufacturing platform, with the main difference being the second B strain;
    - The HA content per strain and MF59 content in aTIV and aQIV are the same.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sol Ruiz Co-Rapporteur: Johann Lodewijk Hillege

The application was received by the EMA on	5 March 2019
The procedure started on	28 March 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	17 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 July 2019

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 February 2020
The CHMP agreed on 2nd list of outstanding issues in writing to be sent to the applicant on	27 February 2020
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	04 March 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	11 March 2020
Working Party experts were convened to address questions raised by the CHMP on The CHMP considered the views of the Working Party as presented in the minutes of this meeting.	02 December 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fluad Tetra on	26 March 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease

Influenza is an infectious acute respiratory disease of global importance that occurs in annual epidemics in the northern hemisphere (NH) and southern hemisphere (SH). The influenza virus is transmitted by respiratory droplets or aerosols containing the influenza virus particles and subsequent inhalation of infectious particles or self-inoculation from a contaminated surface. Clinical manifestation of influenza virus infection is characterized by an abrupt onset of nonspecific respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis.

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, in part due to the age related decline of the immune response (immunosenescence)), pregnant women, younger children (especially up to 24 months of age), and patients with chronic underlying diseases. These groups are considered at risk and represent the priority target for influenza vaccination programmes in the EU.

2.1.2. Epidemiology and risk factors, prevention

Influenza is an infectious acute respiratory disease of global importance that occurs in annual epidemics in the NH and SH during winter months. In temperate climates, influenza generally affects people from November to March in the NH and from May to September in the SH. It can occur all year round in tropical climates.

Influenza in humans can be caused by the influenza virus type A, B and C, of which type A and B viruses are most clinically relevant. Type A viruses are associated with annual epidemics and pandemics, and B viruses contribute to annual epidemics. The type A viruses are further divided into different subtypes, of which the A/H3N2 and A/H1N1 viruses are the most clinically relevant for annual influenza disease burden. For influenza B, only a single type is known to exist, but 2 distinct genetic lineages are identified: Yamagata and Victoria.

Worldwide, annual influenza epidemics result in about 90 million cases with approximately 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths, of which 28,000 to 111,500 occur in children. The main prevention strategy to minimize influenza burden is through annual prophylactic vaccination. Influenza vaccines are designed to protect against illness from the circulating virus strains, and the most commonly used vaccines have been inactivated influenza vaccines (IIV). The World Health Organization (WHO) recommends seasonal influenza vaccination for specific group of people which are more at risk of complications and death: pregnant women, elderly individuals (≥65 years of age), individuals with chronic medical conditions, health care workers, and children aged from 6 months to 5 years. Additionally, some public health authorities are moving towards vaccination strategies to reduce the risk of influenza in all age groups in an effort to decrease overall disease burden and spread to those in the population who are most at risk. In the WHO European Region, an average of over 44,000 deaths occur annually (ranging between 15,000 to 70,000 deaths per season) from influenza related causes with approximately 75% of these deaths occurring in individuals ≥65 years of age.

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. 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.

QIV 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.

2.1.3. Aetiology and pathogenesis

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

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

2.1.4. Clinical presentation

Clinical manifestation of influenza virus infection is characterized by an abrupt onset of nonspecific respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis (Monto et al. 2000). Influenza is generally self-limited and an uncomplicated disease. It can, however, be associated with severe morbidity and mortality in healthy children and certain groups of children and adults who are at increased risk of severe or complicated illness from influenza. Complications such as febrile convulsions, croup, acute otitis media, lower respiratory infections and encephalitis may arise in children as a consequence of the primary influenza infection, or as a result of secondary bacterial infections (Heikkinen et al. 1991). In older adults, pulmonary complications of influenza are most common and include secondary bacterial infection. Among others, acute respiratory infections can exacerbate asthma and chronic obstructive pulmonary disease (COPD) or lead to decompensation of patients with congestive heart failure or diabetes mellitus and subsequently lead to an increased risk of myocardial infarction and cerebrovascular accident (Gordon and Reingold 2018).

2.1.5. Management

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

Vaccination is considered the best approach to lower the burden of influenza disease. Currently, different seasonal inactivated (split virion or subunit) influenza vaccines (quadrivalent and trivalent) are licensed for children, adolescents and adults aged 6 months and older, as well as a live attenuated influenza vaccine licensed for children and adolescents aged 2 years to 17 years of age.

In order to prevent influenza, annual vaccination against influenza is recommended in most risk groups for older adults (≥60 or ≥65 years) and individuals with underlying conditions, such as COPD, heart conditions, diabetes, that leave them at high risk of influenza disease and associated complications. In addition, some countries have general recommendations for influenza vaccination of healthy children.

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).

Further, the protection provided by conventional inactivated influenza vaccines in young children can be more limited than in older children and adults due to the immaturity of their immune system. In older adults, immune responses against conventional trivalent inactivated influenza vaccines have been shown to be lower than in younger adults, and, in line with this, clinical vaccine efficacy estimates were lower in older adults (17% to 53 %) as compared to younger adults (70% to 90%) (Goodwin et al. 2006).

About the product

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is presented as a suspension for injection containing adjuvanted influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, as active ingredients.

Each single dose contains either 7.5 mcg or 15 mcg of haemagglutinin from each of the four influenza virus strains recommended by the WHO and endorsed by CHMP/EMA for the manufacture of influenza vaccine for the current seasons. The adjuvant is MF59C.1 (MF59), which is an oil-in-water emulsion containing squalene as the internal oil phase, sodium citrate – citric acid buffer as the external aqueous phase and polysorbate and sorbitan trioleate as emulsifiers.

The product was developed as 0.25 ml (7.5 mcg HA/strain) and 0.5 ml (15 mcg HA/strain) suspensions for injection in pre-filled syringe (type I glass) with plunger stopper (bromobutyl) and is presented with or without attached needle. During the procedure the Applicant withdrew the paediatric indication; the 0.25 ml strength, which was intended for use in the paediatric population, is therefore not authorised.

Other ingredients are: sodium chloride, potassium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, magnesium chloride hexahydrate, calcium chloride dihydrate and water for injections.

Fluad tetra is also referred to as the adjuvanted quadrivalent influenza vaccine (aQIV) finished product in this application. Initially, the applicant claimed NAS status for the active substance contained in aQIV finished product. However, based on the initial review of the data by CHMP, the active substances contained in the medicinal product Fluad Tetra were not qualified as a new active substance in comparison to the products previously authorised in the European Union. The NAS application was withdrawn by the Applicant. Thus, this application does not now include a new active substance claim.

2.2.2. Active Substance

General information

The active substance (AS) is a sterile suspension containing, predominantly the purified outer membrane proteins, haemagglutinin (HA) and neuraminidase (NA) antigens from the four influenza virus strains recommended every year by the WHO/CHMP. Although there are actually four active substances from each of the four influenza strains, they are collectively referred to as the active substance in this report. Traces of viral envelope parts may be present.

Influenza A viruses are divided into subtypes based on the HA and NA proteins on the surface of the virus. Influenza B is not classified according to subtype. Both the influenza A subtypes and influenza B viruses can be further broken down into different strains that change as the influenza viruses evolve. Each year, the four strains used in the seasonal influenza vaccine consist of one influenza A (H1N1) virus, one influenza A (H3N2) virus, and two influenza B viruses. There are two lineages of the B strains, B Victoria and B Yamagata. Both influenza type A and B viruses undergo minor antigenic variation within a subtype, probably resulting from a series of point mutations and selection. This may effectively challenge subtype-specific immunity within an inter-pandemic period.

Fluad tetra consists of four separate inactivated subunit influenza virus antigen concentrates which are prepared in embryonated chicken eggs, each referred to as a monovalent pooled harvest (MPH). The MPH from each of the four selected viral strains is combined to produce the quadrivalent bulk product.

Manufacture, characterisation and process controls

The four AS are produced and tested by Seqirus Vaccines Ltd (Liverpool, UK). This is also the site of manufacture and release testing for master and working seeds. Testing for mycoplasma for the working seed is performed by a contract laboratory. Appropriate evidence of GMP compliance for all sites has been provided.

Description of manufacturing process and process controls

The monovalent pool manufacturing process can be divided into two primary production stages: production of the inactivated bulk fluid and production of the sterile filtered monovalent pooled harvest (MPH) post sterile-filtration, where some parameters are listed as strain specific.

It is acknowledged that the settings of some process steps need to be amended due to strain-specific characteristics and therefore some flexibility in the process descriptions is considered acceptable. These production/control steps comprise the seed preparation, virus cultivation (incubation conditions), virus inactivation conditions, purification conditions, splitting conditions, and optimisation of the reference standards for the single radial immunodiffusion (SRID) test (identity and potency test).

Briefly, embryonated chicken eggs are inoculated with a virus inoculum prepared from the working seed (WS). Then, the eggs are incubated at an optimum temperature depending on the strain for maximum virus yield. After incubation, the eggs are cooled before harvesting of the allantoic fluid. The harvested allantoic fluid is then centrifuged, filtered, and concentrated. After concentration, virus inactivation is achieved by adding a formaldehyde solution and heating, for a period of time, under strain-specific conditions.

Inactivated allantoic fluid is concentrated and purified (strain-specific concentrations). The inactivated virus is collected and diafiltered.

After diafiltration, the pool is adjusted to give a whole virus concentrate with protein content suitable for the solubilisation process (strain-specific adjustment). The surface antigens are then solubilised using a detergent polysorbate 80 and the antigens split from the virus core using a splitting agent, CTAB. The residual sub-viral particles and residual CTAB are removed. Then, a stabilising solution is added to the subunit supernatant pool which is sterile filtered to produce the MPH (AS) into bio process containers (BPC).

Alternatively, select strains may undergo an alternative pathway in which they are concentrated via an ultrafiltration/diafiltration step, followed by filtration. This final step is required for strains which are not high yielding.

Reprocessing is not claimed. The sterile MPH is transferred to the formulation site via refrigerated (2 to 8°C) trucks. Upon arrival, the integrity of the shipment (including temperature data and controls as well as documentation) is verified and the pools are placed in storage at 2 to 8°C.

A section containing a list of steps that require strain specific modifications together with the general outline of the studies used to investigate the strain specific conditions are included in the CTD.

The batch size for the production of a single monovalent bulk is determined by the number of harvested production eggs. The resulting number of vaccine doses is dependent upon the HA concentration of the individual monovalent bulk lots. The manufacturing process controls are suitably defined.

Control of materials

A list of the compendial raw materials used in the production of monovalent bulk antigen is provided. These materials do not contain any human or animal-derived components, sera, or dyes.

A list of the non-compendial raw materials is also provided.

The chicken embryonated eggs used for the preparation of master and working seeds are produced by chicken flocks free from specified pathogens (SPF). The SPF status of the flock is established according to the Ph. Eur. monograph Chapter 5.2.2 'Chicken Flocks free from Specified Pathogens for the Production and Quality Control of Vaccines'. Production eggs are derived from clinically healthy flocks from several farms, which are periodically audited by Seqirus.

Example certificates of analysis (CoA) for each of the vendor-supplied materials are provided. All non-compendial ingredients are tested to ensure compliance with their specification. Information related to the buffers and solutions used during the manufacturing process is also submitted.

Influenza virus strains are selected, based on the annual regional health authority recommendations, based on surface antigen composition for the quadrivalent vaccine. Influenza virus reference strains, as recommended annually by national regulatory authorities, are provided by WHO collaborating centres and used to prepare master seed (MS) and working seed (WS) lots for each season. MS and WS may be carried over from one season to the next if the same strains are needed.

The MS is produced within the allantoic cavity of Specific Pathogen Free (SPF) eggs using the strain-specific incubation parameters. The MS is tested for haemagglutinating titre and sterility.

The WS represents a single passage from the MS and is produced at a larger scale, again using strain-specific incubation parameters. The WS is tested for HA and NA identity, mycoplasma, sterility and infectivity.

Gene sequence data for influenza strains used for the first time will be provided for future annual strain submissions or as a separate follow-on submission, as for other EU inactivated influenza vaccines.

The provided information on the starting materials is considered appropriate.

Control of critical steps and intermediates

The in-process controls (IPCs) used in the manufacturing process of the AS are reported. Critical process parameters have also been defined.

Relevant process attributes are monitored and controlled by alert/action limits. Overall, the control strategy is considered acceptable.

Process validation

Validation reports of the entire MPH manufacturing process, viral inactivation and splitting efficiency for each influenza strain, together with shipping studies have been provided. The most recent, commercial scale, process validation, encompassing the whole AS production process was performed.

Sufficient information has been provided in support of the inactivation procedures. These procedures will assure a sufficient safety margin in terms of risk of residual infective influenza particles potentially being present in the AS. It is noted that the inactivation characterisation validation studies (for inactivation and splitting) are performed for every new influenza strain which will be introduced following the annual WHO recommendation and these studies will be assessed as part of the Annual Update variation procedure. For process steps that may require strain specific modification, a general outline of the studies used to investigate the strain specific conditions, and the specific modifications required are presented. Overall, the release and in-process data presented demonstrate suitable validation of the AS manufacturing process.

Manufacturing process development

The AS manufacturing process for aQIV has been developed based upon that of the trivalent products - TIV (Agrippal)/adjuvanted trivalent influenza vaccine -aTIV (Fluad) approved in Europe. The AS manufacturing process was developed at Seqirus' predecessor's sites in Italy prior to it being transferred to the commercial manufacturing site, which is now known as Seqirus Vaccines Ltd. (Liverpool, UK).

Following initial development of the manufacturing process, process changes were introduced in the MPH manufacturing process between 1994 and 1997 to improve the purity. Additional changes in the MPH manufacturing process were performed after the 2001/2002 influenza season.

In 2010/2011, the MPH production process through to the pre sterile-filtration stage was transferred from Seqirus' predecessor's sites in Italy to Seqirus Vaccines Ltd (Liverpool, UK) and successfully validated. Therefore, all MPH production since this time has been at Seqirus, Liverpool.

Since 2011, several changes have been introduced in the MPH manufacturing process. The changes introduced since 2011 are described and supported by comparative batch analysis results for batches manufactured with the current and the proposed manufacturing processes. These changes have been proven to have no impact upon the subsequent MPH manufacturing process and are further supported by comparability and process validation. Additional changes to the production process/controls have been introduced after the process performance qualification (PPQ) and clinical batch manufacture. It has been shown that there are no differences in quality attributes between concentrated or non-concentrated product and that all product quality specifications were met.

There is a long manufacturing history leading to significant product/process understanding which is mainly gained by 'traditional' development approaches and, to some extent, by enhanced product development in more recent years using state-of-the-art Quality by Design approaches by performing small scale development studies. The proposed commercial production process and controls can be considered typical for classical influenza vaccine production. Details of the AS batches (from Seqirus Vaccines Ltd. [Liverpool] and Seqirus' predecessor's site in Italy) used in each FP batch produced at

Seqirus' predecessor's site in Italy (clinical batches) and Seqirus Inc. (Holly Springs, US) (PPQ batches) have been presented including the scale of production and date of production. The presented data sufficiently demonstrate comparability between the AS batches used in the FP clinical lots and PPQ batches/commercial process (acknowledging the differences due to strain-specific characteristics).

Characterisation

The AS for each of the four influenza strains selected each year is a sterile suspension containing predominantly the purified outer membrane HA and NA proteins of the influenza virus strains recommended every year by the WHO/CHMP. The viral envelope parts (core proteins) may be present in traces.

The crystal structure of HA has been determined to atomic resolution for the native HA; for HA bound to a number of different receptor analogues; for proteolytic fragments of HA which have gone through the conformational changes required for mediating membrane fusion and for HA complexed with neutralising antibody.

The structure of the NA protein has been determined with structural studies of NA complexed with specific monoclonal antibodies, by electron microscopy, X-ray crystallography amino acid sequencing, and gene sequencing.

HA and NA characterisation studies will be performed on the first three lots of each new influenza strain to confirm the identity, purity, and suitability of the two antigens (HA and NA). The testing program is comprised of: SRID measurements; SDS-PAGE (sodium dodecyl sulphate polyacrylamide gel electrophoresis); and NA identity (and NA enzymatic activity) by enzyme-linked immunosorbent assay (ELISA).

The presented characterisation data on the vaccine antigens is considered appropriate to verify the relevant quality attributes beyond the quality attributes routinely tested for batch release purposes. Although the presented data and characterisation strategy are accepted, the applicant is recommended to extend the information about the analytical procedures used for characterisation purposes, where these do not concern the validated and routinely applied analytical methods for batch release purposes (see recommendations).

The impurities of MPH have been characterised. Impurities were classified as process-related impurities (which include ovalbumin, bioburden, endotoxin, formaldehyde, polysorbate 80, CTAB, antibiotics and hydrocortisone) and product-related impurities (for which adequate control is described). Ovalbumin, formaldehyde, CTAB, and endotoxin are controlled as part of routine MPH release testing. Bioburden is controlled and the AS release specification includes a sterility test. Only traces of hydrocortisone and antibiotics may be present in the AS. In conclusion, the level of control of product-related and process-related impurities meets the Ph.Eur. requirements for influenza vaccine (surface antigen, inactivated) as outlined in Ph.Eur. monograph 07/2019:0869. These impurities have been present in product used in clinical studies.

Specification

The specifications proposed for all MPHs include general tests (appearance), identity tests (haemagglutinin identity and content, neuraminidase identity), and tests for purity (sterility, viral inactivation, non-HA protein, endotoxin, process-related impurities). IPC tests include pH and non-HA protein. The proposed IPCs and specification tests and acceptance criteria are acceptable.

The control AS strategy, including a specification for appearance and the IPC tests, is considered appropriate.

Analytical methods

A description of each analytical method performed is provided. The quality attributes (QAs) routinely tested at the level of the MPH are in line with the Ph.Eur. monograph on Influenza vaccine (surface antigen, inactivated) (07/2019:0869).

SRID is used to determine both HA titre (potency) and identity. The sample being assayed is treated to allow the diffusion of antigens into an agarose gel containing either homologous or heterologous antiserum. In homologous antiserum, the antigens will form a precipitation ring which is then visualised using Coomassie blue staining. The diameter of the precipitation ring is then compared with those obtained using dilutions of known standard reference antigen in order to determine HA titre. Identity is confirmed by precipitation in homologous antiserum and a lack of precipitation in the heterologous antiserum. The HA titre is determined using the parallel line association method. Data generated under the parallel line methodology is further calculated to provide the 95% lower confidence limit.

Description of the analytical procedures and their validation is sufficiently detailed. Appropriate information about the validation of the analytical procedures is provided. Sufficient information has been provided in support of the applied SRID to determine the HA content in the vaccine. The annual SRID verification will be provided as part of all future aQIV annual strain update submissions to document assay performance in support of the campaign product formulation.

Batch analysis

Certificates of analysis (CoAs) of an appropriate number of batches for each influenza strain (H1N1, H3N2, B-Yamagata and B-Victoria lineages) manufactured at commercial scale at Seqirus Vaccines Ltd. (Liverpool, UK) (used in the MPH process qualification) have been provided. All of them comply with the specifications. Batch data comprising three MPHs for each new strain will be provided as part of the Annual Update variation.

Reference materials

Influenza reference antigens for strain characterisation and Influenza antiserum reagents for vaccine standardisation are provided by WHO Collaborating Centres. The reference antigen and antiserum reagents are used to calibrate the haemagglutinin content of inactivated Influenza vaccines by the SRID test. The procedure for SRID reagents qualification is provided and an example reagent qualification report is also included. The antigen/antiserum reagents used during seasonal campaigns will be qualified, and the reagent qualification reports provided.

Container closure

The monovalent bulk is stored in 50-200L Bio-Process Containers (BPCs). The BPCs comply with US and European requirements (Ph.Eur. 3.2.2.1 on Plastic containers for aqueous solutions for parenteral infusions. Certificates of analysis including certificates of irradiation and results from an extractable study have been submitted. It has been justified why additional leaching studies are not needed.

Stability

A shelf life and storage conditions for the AS were proposed by the company. The shelf life was supported by results of stability studies with an appropriate number of lots produced at commercial scale and according to the commercial manufacturing process for each specified strain filled into a container representative of the production containers and stored at the intended storage conditions and at accelerated storage conditions.

In addition, each year an appropriate number of production batches for each strain will be entered into the stability program at the intended storage condition, as well as under accelerated and stressed conditions.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life and storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a combination of MPH, MF59C.1 adjuvant and buffer solutions. The vaccine is presented as a 0.5 mL single dose sterile suspension for injection in a milky-white emulsion, contained in a Type I glass pre-filled syringe with or without an affixed needle. It is an adjuvanted inactivated subunit influenza vaccine.

The surface antigens are isolated from two influenza A subtypes, H1N1 and H3N2, and two influenza B strains, one from the B-Yamagata lineage and one from the B-Victoria lineage. The antigens are the viral surface proteins haemagglutinin and neuraminidase. Each year virus strains from H1N1 and H3N2 and B influenza strains from the B-Yamagata lineage and the B-Victoria lineage are selected for inclusion in the aQIV finished product.

The naturally occurring form of the HA protein, as a component of the influenza virus, is a trimer – three identical "subunits" come together, via non-covalent bonds, to create the active protein. This is the structure that allows the virus to infect a cell and to which the most effective immune response is generated. The surface antigens are formulated with MF59C.1 adjuvant in the final aQIV finished product. The aQIV formulation contains a nominal total of 60 µg of HA antigen per 0.5 ml dose. The excipient concentration is the same as used in Fluad trivalent (aTIV) (including the MF59C.1 adjuvant). The excipients used for the aQIV formulation include: sodium chloride (isotonic aid); potassium chloride (buffer); potassium dihydrogen phosphate (buffer); disodium phosphate dihydrate (buffer); magnesium chloride hexahydrate (stabiliser); calcium chloride dihydrate (stabiliser); MF59C.1 (adjuvant -squalene, polysorbate 80, sorbitan trioleate, sodium citrate); water for injections (diluent). All components comply with the current edition of the USP and Ph. Eur. monographs, as applicable, except for squalene for which no monograph currently exists, and which complies with an in-house specification. There are no novel excipients used. An overfill of 0.1 mL is included to permit withdrawal of the nominal syringe volume. An HA overage is also included (which is specific to a particular strain).

The batches used to perform clinical trials were manufactured at Seqirus' predecessor's site in Italy. Vaccines with different antigenic composition have been used in clinical trials, based on the WHO recommendations for the indicated years. A technical transfer of the formulation, filling, and packaging process of the egg-based adjuvanted influenza vaccine from at Seqirus' predecessor's site in Italy to the commercial FP manufacturing site Seqirus Inc. (Holly Springs, USA), where the batches relevant for the present MAA submission were manufactured, was performed. A comparability strategy was employed between the Italian and Holly Springs sites, addressing facilities and equipment, raw materials, consumables, process parameters and controls, hold times, specifications, product equivalency and critical quality attributes, primary packaging, and leachables and extractables. An analytical comparability assessment confirming that the transfer from the Italian site to the Holly Springs site has not affected the formulation manufacturing process or the quality of the final product was provided.

MF59C.1 adjuvant

MF59C.1 adjuvant is an oil-in-water emulsion with a squalene internal oil phase and a sodium citrate – citric acid buffer external aqueous phase. The emulsion is stabilised by inclusion of two non-ionic surfactants (polysorbate 80-tween 80 and sorbitan trioleate-span). The primary ingredient of MF59C.1 adjuvant is squalene, which is a highly unsaturated hydrocarbon that naturally occurs in many animals and some plants.

The mechanism of action of MF59 to enhance the immune response is well known. Normal tissue-resident monocytes, macrophages and dendritic cells are activated by MF59 in the muscle, and respond by inducing a mixture of chemokines, which results in the migration of immune cells into the injection site. The recruited cells, including monocytes and granulocytes, also produce the same factors on contact with MF59 to further amplify the building chemokine gradient. This results in dramatic signal amplification and a significant influx of phagocytic cells. The higher number of cells available results in more efficient transport of antigen to the lymph nodes. In addition, MF59 may enhance and accelerate the differentiation of cells toward dendritic cells and alter their phenotype. According to the company, no significant interaction between the adjuvant and antigen is expected based on literature and their product development strategy.

MF59C.1 manufacture is performed by Seqirus Inc. (Holly Springs, US). Testing and release is performed by Seqirus Inc. (Holly Springs, US) and Seqirus Vaccines Ltd (Liverpool, UK).

The nature and composition of MF59C.1 has changed throughout the development of the aQIV finished product. The changes in nature and composition of MF59C.1 were introduced before the clinical trials with the aQIV Influenza finished product. Comparability between MF59C.1 manufactured before and after the changes was demonstrated. Comparability studies sufficiently show that these materials are comparable.

MF59C.1 bulk adjuvant is produced at a 350 L scale. Reprocessing is not permitted at any stage of the MF59C.1 bulk adjuvant process. To prepare the emulsion, the components are added to the pre-mixing tank. The material is passed through an inline mixer to form a crude premix. The crude premix is then passed back and forth through a microfluidiser to produce a fine emulsion. The microfluidised bulk is sterile filtered and filled into sterile Flexbag containers. The product contact layer of the flexible bags is compliant with Ph. Eur. requirements for Containers and Tubing for Parenteral Nutrition Preparations and is certified TSE/BSE free. The filtered bulk is stored at 2-8ºC for up to 5 years.

A list of the materials used in the production of MF59C.1 bulk adjuvant is provided. With the exception of squalene, these materials do not contain any human or animal-derived components. Details regarding the specifications and test methodologies used for control are also provided. All other materials are compendial. Appropriate process controls (including critical process parameters and in-process controls) are defined for its manufacture. The MF59C.1 bulk adjuvant process validation has been successfully completed with three consecutive batches at representative scale at Seqirus Inc. (Holly Springs, US). The process validation parameters were within the respective normal operating ranges and met all acceptance criteria specified.

The specifications for release of MF59C.1 include tests for identity (appearance, squalene identity and content), pH, particle size, content of the emulsifying agents, endotoxin and bioburden, and carbonyl content.

Batch analyses for several lots are presented (including validation/stability lots) all produced at Seqirus Inc. (Holly Springs, US). All batches complied with the specifications approved at the time of release. Manufacture has also been appropriately validated.

Sterile MF59C.1 bulk adjuvant is stored at 2-8ºC up to 6 months. Photostability, long-term stability, and accelerated stability studies were performed to establish appropriate storage conditions and shelf life for MF59C.1 Adjuvant Bulk. The shelf-life of MF59C.1 Bulk Adjuvant and storage conditions have been agreed in the dosser, when the bulk adjuvant is stored in flex bags and protected from light. Additional long-term stability studies are currently on-going and accelerated (stability studies have been performed using flex bag containers from the approved vendor on the process validation batches. All parameters tested remained within specification up to the tested time-point. The available data support the proposed shelf-life and storage conditions.

The information provided was acceptable.

Manufacture of the product and process controls

aQIV vaccine finished product manufacturing, packaging, testing and batch control sites are specified in the dossier.

The finished product will be released at:

- Seqirus Vaccines Ltd., Liverpool, UK
- Seqirus Netherlands B.V., Amsterdam, the Netherlands

Prior to implementation of Brexit, Seqirus Vaccines Ltd (Liverpool) will be a site responsible for importation into the EU. Seqirus Netherlands B.V. is the site responsible for EU release testing and batch release. The UK site will need to be removed by variation as a site responsible for importation into the EU at the time of Brexit implementation.

The target batch size for Fluad tetra is specified. aQIV is manufactured as an aseptic formulation in a closed system. Formulation involves the addition of the required four MPHs, phosphate buffered saline (PBS), water for injection (WFI), a stabilising solution and MF59C.1 adjuvant to a formulation vessel. The components are mixed and sampled for testing. The influenza monovalent bulks, PBS buffer and MF59C.1 adjuvant produced from the stored bulk adjuvant are sterile filtered prior to formulation.

During the procedure, the applicant was requested to introduce a point of fill filtration (sterilising filter immediately prior to formulation transfer to an intermediate small volume container, ahead of filling into the final container). The applicant subsequently provided a detailed plan to improve the sterility assurance further for the aQIV filling although it was accepted that the existing information does support sufficient sterility assurance for authorisation (see recommendations). The batch formula for the aQIV finished product depends on the hemagglutinin (HA) content of the monovalent bulk. The HA antigen content of each strain varies from lot to lot. Therefore, based on the HA concentration of each monovalent bulk, the weight of HA antigen for each of four strains is calculated and the amount of the other finished product components are adjusted according to a defined quantitative formulation. Reprocessing is not permitted at any stage of the finished product manufacturing process. Appropriate critical process parameters are provided together with their proven acceptable ranges. These ranges are adequately justified by process development studies.

The process is composed of three process steps each of which has been validated: sterile filtration of MF59C.1; formulation process; filling process. The scope of the process validation at the commercial site, Holly Springs included production of formulated bulk and filling of formulated bulk and was performed at the commercial production scale. Validated analytical methods have been used during process validation.

The influenza strains used for manufacture of the PPQ aQIV batches were described. Process performance qualification runs were performed for the MF59C.1 sterile filtration into bags. All key

process parameters, critical process parameters and performance parameters (critical and non-critical quality attributes), were evaluated for each of the PPQ runs. The hold time for sterile MF59C.1 adjuvant was also validated.

An appropriate number of PPQ runs were successfully executed for finished product formulation and filling. All data generated for the PPQ were assessed against the established acceptance criteria, including CPPs, KPPs, and performance parameters (critical and non-critical quality attributes). Data evaluation included process automation historical data, batch reports, and in-process and release test results. Inspection, labelling, packaging and shipping of filled units was independently qualified and performed during process validation.

The maximum process times and temperatures for the formulation process and filling process and the maximum hold times and storage temperatures of the sterile MF59C.1 and formulated bulk along with a justification of these maximum process times/hold times were provided.

Finished product Container closure system

aQIV is supplied to the market in single dose 0.5 mL pre-filled syringes. It should be noted that according to EU legislation, a type II variation should be submitted for any change in immediate packaging of a sterile biological finished product. The primary container is a barrel made of neutral clear glass, type I (Ph.Eur.) which has a total volume of 1 ml with or without a needle. The plunger stopper is made of latex-free bromobutyl rubber formulation, type I (Ph.Eur.). The syringe without a needle contains a Luer-Lock adaptor to ensure a better and stronger connection of the disposable needle to the syringe.

An extractables and simulation study was performed to identify and to estimate the compounds that may be extracted from the tip caps and plunger stoppers for aQIV syringes upon contact with model solvents. The study concluded that there is negligible toxicological concern for any of the leachables detected in the study as they are present at very low levels.

Product specification

The specifications proposed for release of the final quadrivalent bulk vaccine contains appropriate tests for identity (appearance, haemagglutinin identity for each of the 4 strains, squalene identity), potency (haemagglutinin content for each of the four strains), squalene content, purity (non-HA protein, ovalbumin, CTAB, sterility, absence of live virus, endotoxin), and physicochemical attributes (particle size, osmolality, pH).

The specification for the final filled vaccine includes appropriate tests for identity (appearance, haemagglutinin identity for each of the four strains, squalene identity), potency (haemagglutinin content for each of the four strains), squalene content, purity tests (sterility, endotoxin), physicochemical attributes (particle size, pH), and extractable volume.

The specification for the packed product contains appropriate tests for identity (appearance, haemagglutinin identity for each of the four strains) and pH.

The proposed release specifications for the finished product, filled vaccine and packed product are acceptable and are based on the Ph. Eur. monographs 0869 (influenza vaccine; surface antigen, inactivated) and 0153 (Vaccines for human use) supplemented with tests to control the adjuvant characteristics.

Labelled syringes are packaged in cartons and placed in cases for final storage and shipment.

Analytical methods

There are seven non-compendial analytical procedures used for release testing, all of which have been validated. The compendial methods used have been appropriately validated/verified. See AS analytical section for details of the SRID assay.

Batch analysis

An appropriate number of process performance qualification batches of aQIV were formulated and filled into pre-filled syringes at the Seqirus Inc. (Holly springs, US) site. All the results for the five PPQ batches met the acceptance criteria.

The only process impurities in the finished product are those carried over from the manufacture of MPH and MF59C.1. These impurities are controlled at the MPH and MF59C.1 manufacturing stage. Process-related impurities from the active substance manufacturing process include (but are not limited to) ovalbumin, residual chemicals, including formaldehyde, CTAB, and polysorbate 80. Seqirus updated the Section 3.2.P.5.5 Characterisation of Impurities by the addition of a detailed risk assessment for elemental impurities in accordance with ICH Q3D as part of the D180 response. Appropriate microbial detection assays, sterility and endotoxin assays are in place. All specified impurities have been present in product used in clinical studies. Testing is performed to confirm that no live virus is present, with a specification limit of 'absence of live virus'.

Reference materials

The reference antigen and antiserum reagents used to calibrate the SRID assay are provided every year by WHO Collaborating Centres.

Stability of the product

A 12-month shelf life is proposed for the FP at 2-8°C, protected from light.

The stability evaluation of aQIV in the proposed commercial packaging for an appropriate number of PPQ batches has been completed through 18 months from the date of manufacture at the intended storage condition of 5 ± 3°C and under accelerated and stressed conditions for up to four weeks. The studies were performed in line with ICH Q5C Stability Testing of Biotechnological/Biological Products. All data generated on these PPQ batches under the intended storage condition have met the proposed stability specification and demonstrated no significant change for any quality attributes assessed, which included appropriate stability-indicating parameters.

In addition, supportive data of two 0.5 ml batches used in clinical studies has been presented. It can be concluded that stability of the 0.5 ml presentation is sufficiently substantiated.

Additionally, upon approval, representative commercial batches will also be placed on long-term stability in line with 3.2.P.8.2 Post Approval Stability Commitment.

At 2-8 °C no relevant changes were observed with the exception of the HA content. As can be expected, a decline in potency was observed during storage, particularly for the H1N1 and H3N2 strains. The applicant confirmed that the long-term stability results of the PPQ batches met the proposed EU specification for the HA lower confidence limit of ≥ 80% of label claim.

Each year, three batches of finished product are entered into the stability program at the intended storage condition of 5 ± 3°C, as well as at least one lot under accelerated and stressed conditions.

A 12-month shelf life for the FP at 2-8°C, protected from light, is supported by the provided data.

Post approval change management protocol(s)

Seqirus plans to transfer the finished product formulation and fill/finish operations to other sites post approval.

The company has submitted an adequate post approval change management protocol containing all the information as indicated in EMA/CHMP/CVMP/QWP/586330/2010 Questions and answers on post approval change management protocols.

Adventitious agents

Data of viral inactivation studies carried out in 1993 and 1994 have been presented. These inactivation studies were not performed according to the requirements of Ph. Eur. 0158. The applicant explains that, since 1999, viral inactivation has however been tested according to the Ph. Eur. requirements on the first three production lots of every new strain. This is acceptable. A re-qualification of the inactivation and splitting steps was carried out in 2002/2003 due to an increase in the number of production eggs.

Additional viral clearance studies were also performed many years ago for Avian Leucosis Virus (as relevant virus) and Bovine Adenovirus (as a model for adenoviruses). Based on the results inactivation process parameters were set.

Results of the validation studies for the removal/inactivation of mycoplasma are also presented.

Although the results presented were reassuring, the applicant was requested to update the text to include reference to the current supplier of eggs and the controls implemented at the site. Three egg suppliers are currently approved and qualified. These are now listed in Section 3.2.A.2.7 and the specific requirements presented. The risk assessment addresses the control of the adventitious agents by the most current manufacturing process.

The applicant has followed the EMA GL on Influenza Vaccine –Quality module. The potential risks as regards the introduction of adventitious agents at the different stages (prior) of seed preparation and AS, FP production have been addressed.

With regards to TSE, the only animal derived materials identified are the eggs and the squalene from the adjuvant. Both are considered to pose no TSE risk. This is accepted. In addition, the applicant concludes that the extraction process for squalene, which includes steps for alkaline treatment, elevated temperature and distillation, is expected to inactivate and/or eliminate any viral contaminant. Considering the clinical experience accumulated with this adjuvant, no further requests are considered necessary

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Fluad Tetra (aQIV) is a seasonal surface antigen inactivated influenza vaccine, adjuvanted with MF59C.1. aQIV contains predominantly HA and NA surface antigens from each of the four influenza strains (Type A/H1N1, Type A/H3N2, Type B (Yamagata Lineage) and Type B (Victoria Lineage)), recommended annually by the WHO and subsequently CHMP for the EU market. aQIV includes the adjuvant MF59C.1 (MF59), a squalene-based oil-in-water emulsion.

Overall, the Quality Module 3 is of acceptable quality and most of the deficiencies detected were satisfactorily addressed, with some post approval recommendations.

The manufacturing process and formulation of aQIV are similar to those of the registered adjuvanted trivalent Influenza vaccine (aTIV, Fluad) (some changes have been introduced in the active substance manufacturing process), with the exception of an additional B strain included in aQIV. aTIV has been registered in the EU since 1997 (as well as in many other countries worldwide, including US) for use in adults of 65 years of age and older.

The AS (Monovalent Pooled Harvest, MPH) manufacturing process was developed at Seqirus' predecessor's sites in Italy prior to being transferred (and successfully validated) to Seqirus Vaccines Ltd, (Liverpool, UK) in 2010/2011. Therefore, all MPH production since this time has been at Seqirus, Liverpool. Information on the AS batches used in the manufacturing of the FP batches used in the (pivotal) clinical studies for the current MAA has been presented.

Regarding the analytical procedures used for AS characterisation, the applicant is recommended to extend the description of these analytical procedures, where these do not concern the validated and routinely applied analytical methods for batch release purposes (recommendation 002).

MF59C.1 Bulk Adjuvant is a stable oil-in-water emulsion in which oil droplets are dispersed within a citrate buffer continuous phase. Extensive information is provided on the starting materials/raw materials, (validation of) manufacturing and control of the MF59C.1 Bulk Adjuvant.

The FP (aQIV vaccine) was originally manufactured at at Seqirus' predecessor's site in Italy and all clinical batches were manufactured at this site. Subsequently, as part of the company strategy, the manufacture of the FP along with MF59C.1 adjuvant were transferred to Seqirus Inc. (Holly Springs, US) and this is where the manufacture of the PPQ submission batches took place. The impact assessment of the identified differences between both sites did not give rise to concerns. Additional information was provided confirming that the transfer from the previous site to the Holly Springs site had not affected the formulation manufacturing process or the quality of the final product. Moreover, batch analysis data of the final formulated bulk and final FP of the batches used in the clinical studies could not be found in module 3 of the eCTD. This was considered a major objection as it could not be properly assessed whether the commercial product was similar to the product used in clinical trials. The major objection was solved because the submitted release testing data sufficiently indicated that the Bulk FP and Filled Product produced for the clinical trial and PPQ (and thus commercial production) can be considered comparable, taking into account the different strain composition of the tested vaccine lots. Although the CHMP agrees that the sterility assurance level is sufficient for this type of product, it is noted that the highest level of sterility assurance was not obtained by the chosen sterilisation process conditions. Seqirus has therefore provided a plan to improve sterility assurance by introduction of either a point of fill filtration (sterilising filter immediately prior to formulation transfer to an intermediate small volume container, ahead of filling into the final container) or point of use filtration (sterilising filter immediately prior to transfer to a bulk container into which the entire formulation is filled) in the manufacturing of the finished product (recommendation 003).

Questions were raised on the specification (particularly the SRID potency assay) and FP stability that were appropriately solved. The applicant has committed to submit a study to demonstrate that the FP SRID using a mixed B standard is able to detect degradation of one B strain over the other. As the standards are strain specific, the study can be part of the next annual update (recommendation 004).

A PACMP is included to transfer the finished product formulation and fill/finish operations to contract manufacturing sites.

It is recommended that the applicant reviews the entire CTD and corrects inconsistencies related to the different products mentioned in the dossier (recommendation 001). Finally, based on the initial review of the data, the active substances contained in the medicinal product Fluad Tetra were not qualified as

a new active substance in comparison to the products previously authorised in the European Union (Fluad and Agrippal) for the following reasons:

- The product contains four active substances, not one active substance from a combination of four different strains, as claimed by the applicant. It has to be noted that strains from both lineages of influenza B have been components of approved trivalent influenza vaccines in previous influenza seasons, i.e. no new lineage of influenza B which could be qualified as NAS, is included in the Fluad Tetra composition. The same applies to the two influenza A subtypes.

- The active substance manufacturing process is similar to the one registered for Fluad and Agrippal. This does not result in a novel type of active substance.

- Influenza vaccines have a specific legal provision which permits change of the influenza antigens without leading to a new MA every influenza season even if a new influenza strain is included in an authorised vaccine. Therefore, qualification of the active substance of Fluad Tetra as NAS would thus be inconsistent with the legal provision.

- From a regulatory perspective, an adjuvant is not part of the active substance(s). Therefore the adjuvant MF59C.1 (MF59) in Fluad Tetra cannot be considered in the context of the NAS assessment.

- The active substances in Fluad Tetra do not differ significantly in properties with regard to safety and efficacy from the previously authorised substances.

The CHMP's scientific objection to this claim was also classified as a major objection. At D120 the NAS application was withdrawn by the applicant. Thus, this application does not now include a new active substance claim. This issue has therefore been solved.

In summary, from a quality point of view, Fluad Tetra can be recommended for approval, together with a number of recommendations.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends four points for future quality development.

Area	Number	Description	Classification*
Quality	001	It is recommended that the applicant reviews the entire CTD and corrects inconsistencies	REC
Quality	002	It is recommended that the applicant extends the description of the analytical procedures used for characterisation of the active substance, where these do not concern the validated and routinely applied analytical methods for batch release purposes.	REC

Quality	003	It is recommended that the applicant improves the sterility assurance by introduction of either a point of fill filtration or point of use filtration in the manufacture of the finished product.	REC
Quality	004	It is recommended that the applicant, submits a study to demonstrate that the finished product SRID potency assay, using a mixed B standard, is able to detect degradation of one B strain over the other.	REC

*REC - recommendation

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant has based the non-clinical development for the aQIV on studies performed with: aQIV, Fluad (aTIV), Agrippal (TIV), Aflunov/Foclivia (monovalent pandemic and pre-pandemic surface antigen adjuvanted formulations) and with the adjuvant. Pharmacology studies performed with Fluad formulations are relevant to aQIV because the similar active substance is used in both vaccines, although aQIV contains additional B strain antigen. Both vaccines contain the same amount of adjuvant and the manufacturing process is the same. The addition of antigen from a second B strain is not expected to change the pharmacological effect of the vaccine. Aflunov also contains the same amount of MF59 as aQIV, and the antigens in both vaccines are manufactured using a comparable process. Since the immune response has been adequately characterized with trivalent and monovalent formulations, and data are relevant to aQIV, limited work has been performed with aQIV.

The Table 2 presents the composition of the various related vaccines and adjuvant formulations that are relevant to this dossier. The antigens in all the vaccines listed are manufactured using the licensed egg-based Agrippal process. During the non-clinical development of aTIV, various versions of the adjuvant were tested, including a water-based formulation (referred to as MF59 (water) or MF59-0). This formulation was later optimized by the addition of citrate buffer to provide increased stability (MF59C.1). Results with both formulations are relevant, as immunogenicity and safety are unaffected by the presence of citrate buffer. Both vaccines aQIV and aTIV contain MF59C.1.

Table 1: Formulation overview

Vaccine	Composition
aQIV	Quadrivalent seasonal influenza vaccine, surface antigen, inactivated, MF59C.1 adjuvanted
Fluad (aTIV)	Agrippal + MF59C.1
Agrippal (TIV)	Trivalent seasonal influenza vaccine, surface antigen, inactivated
Aflunov/Foclivia/Focetria (aMIV)	Monovalent pandemic/pre-pandemic influenza vaccine, surface antigen, inactivated, MF59C.1 adjuvanted
Adjuvant	**Composition**
MF59C.1	Squalene, polysorbate 80, sorbitan trioleate, citric acid, sodium citrate, in water
MF59 (water), MF59-0	Squalene, polysorbate 80, sorbitan trioleate, in water

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacodynamic studies of vaccines involve measuring immunogenicity and protection induction by the vaccine. The pre-clinical program has been performed over a long period of time and includes testing seasonal HA antigens from different viral strains. In addition, a summary of studies performed with the monovalent H5N1 pandemic vaccine has also been provided. H5N1 and Fluad contain the same amount of MF59, and the antigens in both vaccines are manufactured using the same process to aQIV. The data obtained with H5N1 and aTIV are considered supportive of the adjuvant role of MF-59.

Pharmacology studies examined the subcutaneous and intramuscular (the one intended to be used in humans) routes and included three animal species (mice, rabbits and ferrets), which are generally considered as adequate models to study influenza virus immunogenicity and viral infection. Several of the studies were performed with an old version of the adjuvant (that lacked citrate buffer). Although this change is not expected to have a major impact on the immunogenicity of the vaccine, these data can formally only be considered supportive of the immunogenicity of the MF-59 adjuvant. The studies performed included analyses of the humoral (using HI and microneutralization assays) and cellular immune response as well as proof of concept (challenge with pathogenic virus) studies.

The pharmacology section included a study in mice (study. SEQ-01) in which the animals were administered different doses of adjuvanted quadrivalent influenza vaccine and with the same doses of HA from a single vaccine strain (either H1N1, H3N2, B Yamagata, or B Victoria) combined with MF59. This study showed that the elicitation of hemagglutinin inhibiting and neutralizing antibodies occurs in a dose-dependent manner. It was observed that MF59-adjuvanted antigens, formulated as aQIV or as individual strains, induced a CD4+ T cell response.

The studies 94-0184 and 93-847 were old non-GLP studies where the animals were immunized subcutaneously (not intramuscular as intended in humans) with TIV with and without an old version of the adjuvant. The studies were indicative of the adjuvant role of MF-59 both in old and young mice and in animals seropositive at baseline due to a previous infection with an influenza virus.

Data from non-GLP studies 94-0307, 94-0214 and 94-0215 were also performed long time ago. The animal model selected was mice. The animals were immunized intramuscularly with different doses of HA antigen with PBS or with an old version of the adjuvant. Antibody responses increased dose dependently. The addition of MF59 increased antibody responses. In studies MF-1/MF-2 2003/04 in which in old and young mice were dosed with the current version of MF-59 wherein different doses of antigen were tested. The data confirmed the previous studies conclusion regarding the capability of the adjuvant employed to enhance the immunization responses.

The challenge experiments described in mice were designed as a continuation of the studies 94-0307, 94-0214 and 94 0215. The mice were challenged with an intranasal infection by wild type influenza virus. The results reveal that mice immunized with the MF59-adjuvanted vaccine were protected against a challenge with an intranasal infection by wild type influenza virus.

Four GLP studies performed in rabbits are recent studies (studies Nos. 486688, 6560-106, 488182 and AB09779) aimed to assess immunogenicity of aTIV or a formulation equivalent to aQIV (60µg per dose), the vaccines showed in all cases to be immunogenic and the antibody titers increased following a second or a third injection of the vaccine. However the studies did not include animals immunized with a non-adjuvanted vaccine so the adjuvant effect of MF-59 could not be tested.

The data provided from the rabbit study in pregnant females reveals that titers were detected in female rabbits, their foetuses, and F1 kits.

A brief summary of the preclinical immunogenicity data obtained with the pandemic H5N1 vaccine has been provided. The studies were performed in several animal species (mice, rabbit and ferret) using the final formulation of the MF-59 adjuvant but the vaccine tested is not a seasonal one since the strain included only one HA antigen from a virus of the H5 subtype (i.e. H5N1). The results from these studies showed that the vaccine was immunogenic and elicited an immune response that protected animals against an intranasal challenge with a homologous H5 viral strain.

Overall, the pharmacology studies are in line with the requirements of current relevant.

Secondary pharmacodynamic studies

No dedicated studies were performed regarding secondary pharmacodynamic. This is endorsed due to the nature of the product.

Safety pharmacology programme

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

Pharmacodynamic drug interactions

No dedicated studies were performed regarding secondary pharmacodynamic. This is endorsed due to the nature of the product.

2.3.3. Pharmacokinetics

In accordance with current guidelines, pharmacokinetic studies are not required for the vaccine assessment. The distribution data obtained in mice with the adjuvant MF-59 do not raise any specific safety concern (Dupuis et al., 1999). The results in mice indicate that MF59 and a soluble antigen gD2 from type 2 herpes simplex virus (HSV) distribute and are cleared independently after intramuscular injection. In another study in mice (Tegenge et al., 2016) in which a formulation similar to MF59 was administered with and without H5N1 antigen suggests that adjuvant AUC was slightly higher in the presence of the antigen. A population pharmacokinetic model based statistical analysis identified body weight and H5N1 antigen as covariates influencing the clearance of squalene.

2.3.4. Toxicology

The toxicology program supporting the clinical development of aQIV consists of one GLP repeat dose rabbit toxicology study which tested a formulation equivalent to aQIV, and GLP studies with aTIV. Toxicology studies performed with aTIV are directly relevant to aQIV because although aQIV contains additional antigen, the same active substance is used in both vaccines, both vaccines contain the same amount of MF59, and the manufacturing process is similar. The addition of antigen from a second B strain does not substantially alter the impurity profile or the tolerability of the vaccine.

The toxicology assessment has been carried out in a number of GLP non-pivotal and pivotal studies in guinea pigs and rabbits. Delayed contact hypersensitivity was assessed using the Magnusson-Kligman Maximization Test in guinea pigs while local and systemic was evaluated in rabbits.

The toxicology program is shown in the

Table 3 below.

Table 2: Outline of toxicity studies

Study type, duration, and number	Route of administration	Species	Compound administered
aQIV equivalent formulation			
Repeat (3) dose GLP Study No. 488182	Intramuscular	Rabbit	aQIV equivalent and aTIV
aTIV formulations			
Delayed contact hypersensitivity GLP Study No. 564110	Intradermal and topical	Guinea pig	aTIV
Repeat (2) dose GLP Study No. 486688	Intramuscular	Rabbit	aTIV
Repeat (2) dose GLP Study No. 6560-106	Intramuscular	Rabbit	aTIV
Repeat (2) dose GLP Study No. 940292	Intramuscular	Rabbit	aTIV
Reproductive and developmental toxicity (4 doses) GLP Study No. AB09779	Intramuscular	Rabbit	aTIV

Single dose toxicity

The lack of single dose toxicity studies is considered acceptable. The repeat dose toxicity assessment is considered sufficient for the evaluation.

Repeat dose toxicity

Three GLP repeat dose toxicity studies are designated non-pivotal. These rabbit studies assessed aTIV compared to TIV or MF59 alone (study 940292), or aTIV compared to aTIV with a second experimental adjuvant (study 6560-106 and study 486688). Two intramuscular doses of vaccine were administered in each of these studies. The results were consistent with the established safety profile for aTIV, and there was no evidence of local or systemic toxicity.

Study 488182 is considered a pivotal GLP study. The animal model was rabbit. The rabbits received saline, Fluad (aTIV), Fluad High B (aQIV equivalent) and Fluad High (H3+IC31) influenza vaccine formulations by 3 intramuscular injections. Although the aQIV was not among the formulations administered, one group received an "aQIV equivalent" since in addition to A/H3N1 and A/H1N1 antigens (15 µg of HA per strain) it contained 30 µg of HA from a single B strain, rather than 15 µg of HA from each of 2 different B strains. Although it differs from the product to be marketed this is considered acceptable for the evaluation since the differences are not expected to result in a significantly dissimilar safety profile. In this study, the aQIV equivalent formulation was comparable to aTIV. The vaccines were well tolerated, and no evidence of toxicity was observed. Results showed no significant systemic toxicity but for some findings in lymph nodes that are compatible with the expected effects of vaccination.

Genotoxicity

No genotoxicity studies were carried out due to the nature of the product and in line with the guidance on vaccines. The results of genotoxicity studies carried out using the adjuvant formulations of MF59 have been submitted (refer to section "other toxicity studies").

Carcinogenicity

The lack of carcinogenicity studies is endorsed due to the nature of the product and in line with current relevant guidelines. In addition, there are not toxicology findings that could be of concern and the final product does not contain any known formulation components or impurities at dose levels that would be expected to be of concern.

Reproduction Toxicity

The reproductive and fertility data (study No. AB09779) reported in rabbits dosed with aTIV including MF59 compared to saline control did not reveal relevant product related concerns. Although the aQIV product was not tested it is not expected that one additional antigen may result in different safety profile. The vaccine evaluated with aTIV vaccine in rabbits was well-tolerated, did not cause maternal or embryofoetal toxicity, was not teratogenic, and had no effects on post-natal development.

Local Tolerance

The local tolerance effects of the product was assessed in rabbits in repeated dose toxicity studies. No significant local tolerance effects were reported, and the findings reported are consistent with the nature of the product. Reported inflammatory changes were partially or fully reversible.

Other toxicity studies

Antigenicity

Delayed contact hypersensitivity potential was assessed in guinea pigs (study No. 564110). The results are suggestive that the product assessed aTIV is not considered a dermal sensitizer (Guinea pig).

Adjuvant

A comprehensive package of GLP toxicology studies has been submitted in order to characterize the potential for local and systemic toxicity of MF59.

In non-clinical studies, MF59 has not been associated with systemic toxicity, and it has a low level of local reactogenicity. In repeat dose rabbit studies, clinical pathology findings of increased fibrinogen and minor inflammatory and degenerative changes at injection sites are consistent with the effects of intramuscular injections of an immunological adjuvant. These findings are reversible within days to 1 to 2 weeks. In repeat dose toxicology studies in dogs, there were no effects on cardiovascular or central nervous system (safety pharmacology) parameters.

MF59 is not genotoxic (Ames test) or clastogenic (mouse micronucleus), is not a dermal sensitizer (Guinea pig), and was not teratogenic (rat and rabbit) or a developmental toxicant (rat).

MF59 is not a new adjuvant, and ample experience exists in relation to human use when combined with influenza antigen made using the current manufacturing process. MF59 has been used in marketed vaccines for more than 20 years, and MF59-adjuvanted influenza vaccines have been

approved for the age indication proposed in this submission. No clinical safety issues requiring nonclinical investigation have been identified. The safety profile of MF59- adjuvanted influenza vaccines has been well established (Black, 2015, Schultze et al., 2008).

2.3.5. Ecotoxicity/environmental risk assessment

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

Not applicable to vaccines according to the guideline Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00).

2.3.6. Discussion on non-clinical aspects

The primary pharmacodynamics of aQIV have been investigated adequately. Studies on secondary pharmacodynamics, safety pharmacology and pharmacodynamics drug interactions have not been performed and are considered not necessary in accordance with the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014).

Pharmacokinetics studies have not been performed with aQIV and are considered not necessary in accordance with the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014).

The toxicology of aQIV has been investigated adequately, including the adjuvant MF59. No effects were observed other than local findings and enlargement of lymph nodes as can be expected after intramuscular injection of a vaccine.

The present application has the non-clinical and clinical support of other vaccines, namely aTIV, that have the same manufacturing process and adjuvant. Data derived from aTIV are considered directly relevant to aQIV because although aQIV contains additional antigen, the same active substance is used in both vaccines, both vaccines contain the same amount of MF59, and the manufacturing process is similar. The addition of an additional antigen has not resulted in a significant change in the pharmacology or toxicology of the product.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers the vaccine is considered approvable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 3 Overview of clinical studies for the paediatric indication development

Study ID	**No. of study centres / locations**	**Phase** **Design** **Population**	**Study Objective**	**Test Products,** **No of Subjects:** Enrolled / Completed	**Sex, Male / Female** **Mean Age (SD)**	**Duration Study Dates (FSFV, LSLV)**
Pivotal Efficacy Study						
V118_ 05 (2013/2014 & 2014/2015)	146 centres in USA, Canada, Finland, Italy, Philippines, Poland, Spain, Taiwan, Thailand	Phase 3 Stratified, randomized, observer-blind, active controlled Children 6 to <72 months of age, healthy or at high risk of complications from influenza	Efficacy, immunogenicity and safety	aQIV: 5352 / 4568 Comparator: 5292 / 4545	5411 / 5233 38.2 months (18.42 months)	Nov-2013, Apr-2016
Revaccination studies						
V118_05E1 (2014/2015)	30 centres in USA and Finland	Phase 3 Randomized, observer-blind, active controlled Children, healthy or at high risk of complications from influenza, who completed V118_05 (Season 1)	Immunogenicity and Safety	aQIV: 318 / 304 QIV-1: 289 / 258	281 / 326 43.4 months (18.35 months)	Oct-2014 Jan-2016
V118_05E3 (2015/2016)	17 centres in Finland, the Philippines and Thailand	Phase 3 Randomized, observer-blind, active controlled Children, healthy or at high risk of complications from influenza, who completed V118_05 (Season 2)	Immunogenicity and Safety	aQIV/aQIV: 403 / 400 aQIV/QIV-1: 403 / 401 QIV-1/aQIV: 401 / 399 QIV-1/QIV-1: 394 / 391	831 / 770 53.3 months (17.09 months)	Jan-2016 May-2017

Study ID	No. of study centres / locations	Phase Design Population	Study Objective	Test Products, No of Subjects: Enrolled / Completed	Sex, Male / Female Mean Age (SD)	Duration Study Dates (FSFV, LSLV)
Supportive aTIV immunogenicity studies						
V70_29 (2011)	32 centres in Argentina, Australia, Chile, Philippines, South Africa	Phase 3 Stratified, randomized, observer-blind, active controlled Children 6 to <72 months of age	Immunogenicity and Safety	aTIV: 3136 / 2983 TIV-1: 1478 / 1389 TIV-2: 1486 / 1408	3080 / 3024 33.7 months (18.1 months)	Apr-2011, Jul-2012
V70_50 (2014/2015)	3 centres in Mexico	Phase 2 Randomized, observer blind, active controlled Healthy children 6 to <72 months of age	Immunogenicity and Safety	aTIV: 144 / 139 TIV-1: 143 / 134	147 / 140 29.8 months (18.6 months)	Oct-2014 May-2015
V70P2 (2006/2007)	1 centre in Finland	Phase 2 Randomised 1:1 controlled observer blind Unprimed healthy children aged 6-<36 m	Immunogenicity and safety	aTIV / TIV (Vaxigrip): 1st inj 130 / 139 2nd inj 117 / 127	156 / 125 20.8 months (8.7 months)	Nov-2006 Aug-2007
V70P6 (2008)	5 centres in Guatemala	Phase 2 Randomised (1:1) controlled observer blind Unprimed healthy children aged 6-<60 m	Immunogenicity and safety	aTIV/ TIV (FLuzone): 1st inj 180 / 180 2nd inj 172 / 168	194 / 166 21.6 months (14.4 months)	Jan-2008 Oct-2008
V70_34	2 centres in Belgium	Phase 2 Randomized, observer-blind, parallel group, active controlled Unprimed health children aged 6 to <36 months	Immunogenicity and Safety	aTIV: 43 / 40 TIV-2: 41 / 38	50 / 34 20.8 months (9.1 months)	May-2011 Feb-2012

Table 4: Overview of clinical studies for the elderly indication development

Study ID **Influenza season**	**No. of study centres / locations**	**Phase** **Design** **Population**	**Study Objective**	**Test Products,** **No of Subjects:** Enrolled / Exposed / Completed	**Duration Study Dates (FSFV, LSLV)**
Pivotal studies					
V118_20 2017/2018 NH	20 centres United States	Phase 3 Randomized, Double-Blind, Controlled, Clinical Study Adults ≥65 years of age	Safety and immunogenicity of aQIV vs. aTIV-1(Fluad) and aTIV-2 (containing the alternate B strain)	aQIV: 889 / 888 / 881 aTIV-1 (Fluad): 445 / 444 /440 aTIV-2: 444 / 444 / 439	Duration: 6 months following a single vaccination Dates: 17 OCT 2017 to 17 MAY 2018
V70_27 2010/ 2011 NH 2011 SH	38 centres Colombia Panama The Philippines United States	Phase 3 Randomized, Controlled, Observer-Blind, Clinical Study Adults ⩾65 years of age	Lot to lot consistency of aTIV; and safety, tolerability, immunogenicity of aTIV vs. TIV	aTIV: 3552 / 3541 / 3361 TIV (Agriflu): 3552 / 3541 / 3356	Duration: 12 months following a single vaccination Dates: 13 AUG 2010 to 16 NOV 2011
Supportive studies (aQIV and aTIV)					
V118_18 2016/2017 NH 2017 SH	89 centers Bulgaria Colombia Czech Republic Estonia Latvia Lithuania Malaysia Philippines Poland Romania Thailand Turkey	Phase 3 Randomized, Observer Blind, Controlled, Multicenter Clinical Study Adults ⩾65 years of age	Efficacy, Safety and Immunogenicity of aQIV vs Non-influenza Vaccine Comparator	aQIV: 3394/3379/3263 Comparator: 3396/3382/3273	Duration: 12 months following a single vaccination Dates: 30 September 2016 to 23 July 2018
V7P3 1992/1993	Italy	Phase 2 Randomized parallel, observer-blind single centre study Adults ⩾65 years of age	Safety, tolerability and immunogenicity of aTIV vs. TIV	46 aTIV (sv) 46 TIV (Agrippal)	Dates: 26 Nov 1992 to 05 May 1994
V7P5 1993/1994	Italy	Phase 2 Observer-blind randomized parallel single centre clinical study Adults ⩾65 years of age	Safety, tolerability and immunogenicity of aTIV in syringe (ss) vs. TIV vs. aTIV in syringe-vial (sv)	106 aTIV (ss) 106 aTIV (sv) 105 TIV (Agrippal)	3 Nov 1993 to 09 Jun 1994

Study ID **Influenza season**	**No. of study centres / locations**	**Phase** **Design** **Population**	**Study Objective**	**Test Products,** **No of Subjects:** Enrolled / Exposed / Completed	**Duration Study Dates (FSFV, LSLV)**
V7P7 1993/1994	Lithuania	Phase 2 Randomized, observer-blind multicentre clinical study Elderly ⩾65 years of age nursing home residents who were at risk for influenza	Safety, tolerability and immunogenicity of aTIV vs. TIV	109 aTIV 105 TIV (Agrippal)	06 NOV 93 to 31 MAR 94
V7P8 1994/1995	Italy	Phase 2 Parallel, observer blind multicentre clinical study Adults ⩾65 years of age	Safety, tolerability and immunogenicity of aTIV vs. TIV	204 aTIV (ss) 104 TIV (Agrippal)	10 Oct 1994 to 19 May 1995
V7P25 1995/1996	The Netherlands	Phase 3 Observer-blind, randomized multi-center clinical study Institutionalized elderly ⩾65 years of age	Safety, tolerability, and immunogenicity of aTIV vs. TIV	142 aTIV 141 TIV (Vaxigrip)	20 Oct 1995 to 15 May 1996
V7P35 1997/1998	Italy	Phase 4 Single-blind, multicentre, randomized parallel clinical study Adults ⩾65 years of age	Safety, effectiveness and immunogenicity of aTIV vs. TIV	9171 aTIV 4550 TIV (Influvac)	29 Sep 1997 to 27 Apr 1998
Supportive aTIV Revaccination Studies in Subjects ⩾ 65 years of age					
V7P3X1, V7P3X2 1993/1994 1994/1995	Italy	Phase 2 Randomized parallel, observer-blind single centre study Adults ⩾65 years of age	Safety, tolerability and immunogenicity of aTIV vs. TIV	39 aTIV (sv) 35 TIV (Agrippal) 35 aTIV (ss) 32 TIV (Agrippal)	27 SEP 94 to 28 MAR 95
V7P5X1, V7P5X2 1994/1995 1995/1996	Italy	Phase 2 Prospective, observer-blind, randomized,	Safety, tolerability, and immunogenicity of aTIV (ss) vs. TIV vs.	80 aTIV (ss) 63 aTIV (sv) 73 TIV (Agrippal) 62 aTIV (ss) 53 aTIV (sv)	12 OCT94 to 08 MAY 95 16 Oct 1995 to 30 apr 1996

Study ID Influenza season	No. of study centres / locations	Phase Design Population	Study Objective	Test Products, No of Subjects: Enrolled / Exposed / Completed	Duration Study Dates (FSFV, LSLV)
		parallel, single-center study. Adults ⩾65 years of age	aTIV (sv)	55 TIV (Agrippal)	
V7P7X1 1994/1995	Lithuania	Phase 2 Randomized, observer-blind multicentre clinical study Elderly ⩾65 years of age nursing home residents who were at risk for influenza	Tolerability and immunogenicity of aTIV vs. TIV (clinical surveillance for efficacy in subset of patients)	75 aTIV 64 TIV (Agrippal)	20 OCT 94 to 28 APR 95
V7P8X1, 1995/1996	Italy	Phase 2 Parallel, observer blind multicentre clinical study Adults ⩾65 years of age	Safety, tolerability, and immunogenicity of aTIV vs. TIV	148 aTIV 69 TIV (Agrippal)	27 Sep 1995 to 01 Apr 1996
V7P25X1 1996/1997	The Netherlands	Phase 2 Observer-blind, randomized multi-center clinical study Institutionalized elderly ⩾65 years of age	Safety, tolerability and immunogenicity of aTIV vs. TIV	87 aTIV 89 TIV (Vaxigrip)	30 Sep 1996 to 29 Apr 1997

Planned Studies

V118_24, a clinical disease endpoint trial in subjects 65 years of age and older with Fluad Quadrivalent (this is the tradename of Fluad Tetra in the US). This study is planned to be completed in March 31, 2024.

2.4.2. Pharmacokinetics

Pharmacokinetic studies were not conducted in the development program of aQIV and aTIV, in line with current guidelines. Pharmacokinetic studies are not required for influenza vaccines as the kinetics properties of vaccines do not provide useful information for establishing adequate dosing recommendations.

2.4.3. Pharmacodynamics

Mechanism of action

Fluad Tetra provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine. Fluad Tetra induces humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses.

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

Specific levels of hemagglutination inhibition (HI) antibody titers post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus, but the HI antibody titers have been used as a measure of vaccine efficacy. Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. As indicated in this guideline the pharmacodynamic profile for vaccines is defined by its immunogenicity profile. These data are discussed in the "Clinical Efficacy" section.

Fluad Tetra contains the adjuvant MF59C.1 (MF59), which is designed to increase and broaden the antigen-specific immune response and to extend the duration of the immune response.

2.4.4. Discussion on clinical pharmacology

The current formulation of aQIV, presented as a thimerosal-free, sterile suspension for injection, in prefilled syringes consists of 2 admixed components: inactivated antigens and MF59 in a citrate buffer. aQIV is a quadrivalent seasonal surface antigen, inactivated, adjuvanted influenza vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. aQIV contains influenza virus surface antigens (hemagglutinin [HA] and neuraminidase) of each of the 4 influenza virus strains (A/H1N1, A/H3N2, B/Yamagata, B/Victoria) that are recommended by the World Health Organization (WHO) for use in the vaccination campaigns in advance of the respective northern and southern hemisphere seasons. aQIV has the same antigen content as aTIV, with an additional influenza B strain from the alternate lineage as the one contained in the licensed aTIV. The manufacturing process and formulation of aQIV and Fluad (aTIV) are the same, with the exception of an additional B strain included in aQIV. Therefore, clinical study experience with aTIV provides relevant and valuable data for assessment of the overall immunogenicity and safety of aQIV.

The MF59 component of aQIV is an oil-in-water emulsion composed of squalene stabilized by a water-soluble surfactant (polysorbate 80, also known as Tween 80) and an oil-soluble surfactant (sorbitan trioleate, also known as Span 85), in a low ionic strength buffer. The MF59 adjuvant was developed in the 1980s and clinical studies using pandemic influenza antigens and seasonal influenza antigens demonstrate that MF59 adjuvanted vaccine increases the humoral response to a diverse set of influenza strains (Del Giudice et al. 2006; Ansaldi et al. 2008; Galli et al. 2009; Ansaldi 2010). The antigen dose and vaccination schedule were based on approved trivalent or quadrivalent inactivated influenza vaccines at the time of conduct of the clinical development program, i.e. the aTIV/aQIV formulations used contained either 7.5 or 15 µg of hemagglutinin (HA) of each viral strain per 0.25 or 0.5 mL dose, respectively. The formulation of the final product is in compliance with the European Pharmacopoeia (monograph 0869). Throughout this application, the terms aTIV and aQIV refer to the formulation of MF59-adjuvanted TIV and MF59-adjuvanted QIV, as described here.

The use of the hemagglutination inhibition (HI) assay as the primary assay to assess vaccine immunogenicity in clinical trials is in line with the recommendations of the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014). While HI titers are not a true surrogate marker, it has been widely shown that higher HI titers tend to correlate with better protection. The CHMP guideline on influenza vaccines also recommends measuring the immunogenicity of the vaccine in terms of Cell Mediated Immunity (CMI), Microneutralization (MN) and Anti-Neuraminidase (anti-NA) assays in a subset of individuals. These assessments were performed on at least one study. The MN, anti-NA and CMI assays were performed by the same laboratory, which avoids inter-laboratory bias that could result if different testing laboratories had been used. For pivotal trial V118_05 and the revaccination studies V118_05E1 and V118_05E3 all HI testing was performed at the same laboratory whereas for other supportive studies with aTIV and the dose-finding study (V104P2) the HI tests were performed at different laboratory. Although this aspect does not question the validity of the results for these trials, it should be taken into account when comparing HI results from these different studies. The validation report provided in relation to the HI test performed by the lab was included in the dossier and concluded that the test was satisfactorily validated. Moreover, validation reports for microneutralisation assay to detect functional antibodies that prevent infection of cells in tissue culture; and enzyme-linked lectin assay (ELLA) to measure Neuraminidase antibody titers, were submitted. Assay validation reports of the HI assay used for the pivotal aQIV study V118_20 and the key supportive aTIV study V70_27 (elderly indication) were also provided and concluded that the test was validated.

Comparing HI titers in terms of GMTs is considered adequate. Similarly, the definition of seroconversion rate defined as, the percentage of subjects achieving either: 1) a prevaccination (baseline) HI titer <1:10 and postvaccination HI titer ≥1:40 after vaccination; or 2) a prevaccination (baseline) HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer) is also considered appropriate.

The former criteria recommended by CHMP to assess immunogenicity of influenza vaccines (CHMP guidance for licensure of seasonal influenza vaccines, 1997) and the current criteria recommended by CBER (2007) for paediatric population have been used for some of the trials included in this Marketing Authorisation Application (MAA). It is considered that the data on fulfilment of these two criteria (CBER and CHMP) are deemed informative, but not critical for the immunogenicity assessment of the vaccine, since the CBER criteria are not a requirement for approval in the EU, and that the CHMP criteria are (since a few years ago) no longer required for approval of influenza vaccines (see current CHMP guideline: The Guideline on Influenza Vaccines - Non-clinical and Clinical Module (EMA/CHMP/VWP/457259/2014). Moreover, it should be noted that there have never been CHMP criteria for subjects younger than 18 years of age.

2.4.5. Conclusions on clinical pharmacology

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

2.5. Clinical efficacy

2.5.1. Dose response study

Paediatric indication development

The only dose-finding study was the trial V104P2.

Study V104P2 was a randomized, observer-blind, dose-ranging, multicentre, incomplete factorial design study in unprimed healthy children from 6 months to less than 3 years of age. The study was designed to evaluate the safety, tolerability and immunogenicity of different combinations of two different doses of trivalent inactivated influenza vaccine, different doses of MF59 and /or a second influenza B strain. There were 410 subjects randomised in 17 study groups. This was an explorative study. The results of this study are suggestive of the following:

- The addition of adjuvant resulted in a clear increase in GMTs and further small increases in GMT with increasing MF59 dose. Although pairwise comparisons between antibody responses induced by half the MF59 adjuvant and antigen of the adult adjuvanted vaccine and lower MF59 dose levels (¼ and ⅛) did not reach statistical significance, point estimates were generally in favour of the ½ dose level, especially against the B strain, the proposed dose for children 6-36 months.
- The presence of adjuvant (any level) improves the response to heterologous strains for influenza A/H1N1, H3N2 and influenza B after two vaccinations. This observation regarding the "paediatric" formulation of Fluad (7.5µg TIV+½MF59) is particularly relevant considering the prevalence of "drifted" or mismatched B strain disease in young children.
- The reactogenicity data provides no suggestion that reactogenicity might increase with adjuvant or antigen dose. Similarly, there is no apparent pattern of increased rates of unsolicited AEs, including possibly related AEs with increasing adjuvant content or increase antigen dose. However numbers are very low and differences in patterns of adverse events are unlikely to be detected in this study.

The WHO currently recommends that vaccine-naive children from 6 months through 9 years of age should receive 2 vaccine doses separated by ≥4 weeks (World Health Organization 2012). Additionally, at the time of study conduct, the available influenza vaccines were recommended at a dose of 0.25 mL in children <3 years and at a dose of 0.5 mL in children ≥3 years of age. At this moment, most influenza vaccines indicated in this age group leave the decision to prescribers to give a 0.25 mL or a 0.5 mL dose.

Subjects in the pivotal aQIV study V118_05 were vaccinated according to the dosing and vaccination schedule in Table 6.

In the context of this MAA, the following definitions apply:

- Vaccine non-naïve (previously vaccinated) subjects were defined as those subjects that received 2 or more doses of seasonal influenza vaccine since July 1, 2010.
- Vaccine naïve (not previously vaccinated) subjects were defined as subjects that had not received 2 or more doses of seasonal influenza vaccine since July 1, 2010 or who did not know their influenza vaccination history.

Table 5 aQIV paediatric dosing schedule

Age	Dose	Schedule
6 to <36 months	One or two[a] doses, 0.25 mL each	If 2 doses, administer at least 4 weeks apart
36 to <72 months	One or two[a] doses, 0.5 mL each	If 2 doses, administer at least 4 weeks apart

Abbreviations: aQIV = adjuvanted quadrivalent influenza vaccine; WHO = World Health Organization.

[a] 1 or 2 doses depending on vaccination history as per WHO recommendations on prevention and control of influenza with vaccines.

Elderly indication development

In two dose finding studies (V104P3 and V7P38) in elderly, different dosages of antigen and adjuvant were evaluated. Study V104P3 tested different dose levels of MF59 adjuvant (none, ¼, ½, full) and two different levels of A/H3N2 antigen (15µg vs 30µg). Study V7P38 tested different dose levels of MF59 adjuvant (none, ½, full) and two different levels of antigen (7.5µg vs 15µg). There were numerous immunogenicity objectives related to identifying the optimal adjuvant-antigen dose combination in comparison with the marketed formulation (Fluad, 15µg TIV + MF59).

In both studies, the addition of the adjuvant led to an increase in immune response, but also to an increase of reactogenicity. In study V7P38, seroconversion rates were highest in the aTIV (100% MF59, 15µg HA/strain) group, Fluad. Study V104P3 showed a similar picture, however the group receiving a higher amount of A/H3N2 antigen had a higher response to A/H3N2 and for this strain there was no difference between the 50% adjuvant and 100% adjuvant group. Immunogenicity was also to be evaluated against heterologous influenza strains. The addendum presenting results for heterologous strains was not included in the current submission.

The addition of the adjuvant resulted in a higher reactogenicity, with the highest rate of pain reported for the groups who received the highest level of adjuvant. As most adverse events were mild or moderate, the benefit of the increased immune response weighs out against the risk of the increased reactogenicity. Therefore these studies support the current proposed dose of antigen and adjuvant.

2.5.2. Main studies (paediatric indication)

The clinical development program of aQIV includes 9 clinical studies with aQIV and aTIV conducted in subjects 6 to <72 months of age.

- One aQIV pivotal study V118_05
- Five supportive aTIV studies (studies V70_29, V70_50, V70P2, V70P6, and V70_34)
- Two aQIV revaccination studies (studies V118_05E1 and V118_05E3)
- One aQIV dose-finding study (V140P2)

2.5.2.1. V118_05

Study V118_05 was a Phase 3, observer-blind, stratified, randomized, group sequential, multicentre study to evaluate the efficacy, immunogenicity and safety of aQIV compared to nonadjuvanted comparator influenza vaccine in children from 6 to <72 months of age. The study occurred between November 2013 and April 2016 across 9 countries (Canada, Finland, Italy, Philippines, Poland, Spain, Taiwan, Thailand, and USA).

Methods

Study Participants

A total of 10,644 subjects ≥6 to <72 months of age were enrolled/randomized to receive aQIV or comparator vaccine. The subjects were male and female individuals ≥6 to <72 months of age, and healthy or at high risk of complications from influenza.

Inclusion Criteria

In order to participate in this study, all subjects had to meet all of the inclusion criteria described as follows:

1. Children, males and females, healthy or at high risk of complications from influenza, between ≥6 to <72 months of age.
2. Documented consent provided by the individual's parent(s)/legal guardian(s) according to local regulatory requirements **after** the nature of the study had been explained to them.
3. Subject's and/or subject's parent(s)/legal guardian(s) able to comply with all study procedures, and available for all clinic visits and telephone, email and/or text message (SMS) contacts scheduled in the study.
4. Subject's parent(s)/legal guardian(s) willing to allow for serum samples to be stored beyond the study period, for potential additional future testing to better characterize immune response.

Exclusion Criteria

Subjects who met any of the following criteria were not eligible to participate in the study:

1. Children, whose parent(s)/legal guardian(s) were not able to comprehend and to follow all required study procedures for the whole period of the study.
2. History of Guillain-Barré Syndrome, epilepsy, or history of convulsions (excluding febrile convulsions).
3. Children with any fatal prognosis of an underlying medical condition (<12 month life expectancy).
4. Children who had any medical condition meeting the definition of the AESI defined for the purposes of this study.
5. Children hospitalized at the time of enrollment.
6. History of any anaphylaxis, serious vaccine reactions, or hypersensitivity to any vaccine component, to eggs (including ovalbumin), and chicken protein, latex.
7. Children of research staff directly involved with the clinical study or who were otherwise related to research staff or had household members who were research staff. Research staff individuals with direct or indirect contact with study subjects, or study site personnel who had access to any study documents containing subject information. This would include receptionists, persons scheduling appointments or making screening calls, regulatory specialists, laboratory technicians, etc.
8. Fever (i.e., body temperature measurement ≥38°C [≥100.4°F]) measured preferably orally. This was not an absolute exclusion criterion; the individual could have been enrolled/vaccinated once he/she was free of fever for at least 3 days.
9. Children who had received vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment into this study. Depending upon the duration of enrollment, children with this exclusion criterion could have been eligible for enrollment into the study once either 14 days (for inactivated vaccine administration) or 28 days (for live vaccine administration) had passed.
10. Children who had received antipyretic medication within the past 24 hours prior to vaccination. The subject could have returned for vaccination after a period of 24 hours had passed since the administration of an antipyretic.
11. Receipt of another investigational agent within 30 days prior to enrollment or before completion of safety follow-up period in this or in another study, or unwillingness to refuse to participate in another clinical study through the duration of this study.
12. Children who had been immunized with any influenza vaccine (licensed or investigational) or with laboratory-confirmed influenza within 6 months prior to enrollment.

13. Children's parent(s)/guardian(s) who were unwilling to be contacted by the phone for the safety phone calls or phone, email or text message (SMS) for the active influenza surveillance.
14. Individuals who had been diagnosed with any disorders in growth such as failure to thrive (FTT) or short stature.
15. Subjects who had previously participated in the V118_05 study.

Treatments

Three vaccines were used in the trial. The candidate vaccine was:

1) aQIV: A 0.5 mL dose of aQIV (MF59C.1 adjuvanted influenza vaccine) administered to subjects ≥36 months (or 0.25 mL for subjects <36 months), containing nominally 15 µg (or 7.5 µg for subjects <36 months) of HA of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 µg (or 30 µg for subjects <36 months) of HA in the vaccine. The strain composition was that recommended by the World Health Organization (WHO) for QIV contemporaneous to the timing of the study. The NH formulations of the vaccines used in the study (Season 1: 2013/2014; Season 2: 2014/2015) contained A/California/7/2009 pdm09-like virus (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012 (B/Yamagata) and B/Brisbane/60/2008 (B/Victoria). The vaccine strain composition was unchanged between Seasons 1 and 2. The 0.25 mL vaccine formulation consists of 50% of all vaccine components of the 0.5 mL vaccine formulation.

The two non-adjuvanted comparator vaccines used were:

2) Fluzone (TIV): A 0.5 mL (or 0.25 mL for subjects <36 months) dose of Fluzone containing nominally 15 µg (or 7.5 µg) of HA of each of the 2 influenza A strains and of one influenza B strain for a total of 45 µg (or 22.5 µg) of HA in the vaccine.
3) Fluzone (QIV): A 0.5 mL (or 0.25 mL for subjects <36 months) dose of QIV Fluzone containing approximately 15 µg (or 7.5 µg) of HA of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 µg (or 30 µg) of HA in the vaccine.

   NH formulations of the vaccines were used in the study. A/California/7/2009 pdm09-like virus (H1N1), A/Texas/50/2012 (H3N2) and B/Massachusetts/2/2012 (B/Yamagata) were included in the comparator vaccine used in Season 1. A/California/7/2009 pdm09-like virus (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012 (B/Yamagata) and B/Brisbane/60/2008 (B/Victoria) were included in the comparator vaccine in Season 2.

Based on previous influenza vaccination history (vaccine status), subjects received either 1 (vaccine on Day 1 for vaccine non-naïve subjects) or 2 doses (vaccine on Days 1 and 29 for vaccine naïve subjects) of either aQIV or non-adjuvanted comparator (Fluzone TIV in the first influenza season, and Fluzone QIV in the second season).

Study V118_05 was conducted over 2 consecutive influenza seasons using the NH vaccine formulations (Season 1: 2013/2014; Season 2: 2014/2015). For Season 1, aQIV was compared to TIV-1, and for Season 2, QIV-1 was used as a comparator.

Objectives

The primary and secondary relative efficacy objectives were measured in all subjects in relation to cases occurring at ≥21 days and ≤180 days after the last vaccination (unless specified otherwise) or until the end of the influenza season whichever was longer. In all cases, efficacy was determined on influenza cases caused by any of the influenza strains related to the 2 A subtypes and the B lineage(s) common

to adjuvanted quadrivalent influenza vaccine (aQIV) and trivalent influenza vaccine (TIV) (i.e., A/H1N1, A/H3N2 and B/Yamagata during the first influenza season), and common to aQIV and quadrivalent influenza vaccine (QIV) (i.e., A/H1N1, A/H3N2 and both B lineages during the second season and through to the end of the study). Data from all seasons were combined.

The **Primary Efficacy Objective** was to demonstrate the relative efficacy of aQIV compared to non-adjuvanted comparator as determined by the proportion of subjects with first-occurrence reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months of age.

The following **secondary objectives** were evaluated in all subjects and in the following age groups: ≥6 to <24 months of age, ≥6 to <36 months of age and ≥36 to <72 months of age.

- To evaluate the relative efficacy of aQIV compared to non-adjuvanted comparator as determined by the proportion of subjects with first-occurrence RT-PCR-confirmed influenza A and/or B of any influenza strain.
- To evaluate the relative efficacy of aQIV compared to non-adjuvanted comparator as determined by the proportion of subjects with first-occurrence influenza caused by culture-confirmed strains A and/or B regardless of antigenic match to those contained in the vaccines, antigenically matched to those contained in the vaccines and antigenically unmatched to those contained in the vaccines.

The following secondary objectives on first-occurrence RT-PCR and first-occurrence culture-confirmed influenza as described above were evaluated in subjects ≥6 to <72 months of age:

- To evaluate the relative efficacy of aQIV compared to non-adjuvanted comparator in subjects at high risk of influenza complications.
- To evaluate the relative efficacy of aQIV compared to non-adjuvanted comparator in (vaccine) naïve subjects and non-naïve subjects separately.

The following secondary objectives were intended to evaluate early efficacy:

- To evaluate the relative efficacy of aQIV compared to non-adjuvanted comparator as determined by the proportion of subjects with first-occurrence RT-PCR-confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months of age at ≥7 days and at ≥14 days after the first vaccination up to the day of the second vaccination in vaccine naïve subjects only; occurring at ≥7 days and ≤21 days after the last vaccination, in all subjects; occurring at ≥7 days to ≤180 days after the last vaccination or until the end of the influenza season, whichever was longer in all subjects.

The relevant **immunogenicity objectives** combine data from both Season 1 and Season 2 for the overall age group of 6 to <72 months. As the vaccine composition remained unchanged this is possible. For strain comparisons in the combined seasons, B/Victoria results from Season 2 only were taken into account in view of the lack of this strain from the comparator vaccine in Season 1. In addition, subgroup analysis by season, by age group (≥6 to <24 months of age, ≥6 to <36 months of age, ≥36 to <72 months of age) and by season and age group are presented. The main immunogenicity objective was to evaluate the HI response according to the CBER criteria defined for children. Therefore the focus is on the additional immunogenicity objectives, which were:

- To demonstrate non-inferiority and superiority of HI antibody responses to aQIV vs. TIV/QIV against each of the 3 strains contained in TIV (A/H1N1, A/H3N2 and B/Yamagata) and against each of the 4 strains as contained in QIV (A/H1N1, A/H3N2, B/Yamagata and B Victoria) in terms of ratio of geometric mean titre (GMT) and differences in the proportion of subjects with seroconversion (SC) 21 days after the last vaccination in subjects ≥6 to <72 months of age.

- To compare the antibody response 180 days after the last vaccination to aQIV and TIV/QIV to each of the 3 strains contained in TIV (A/H1N1, A/H3N2 and B/Yamagata) and against each of the 4 strains as contained in QIV (A/H1N1, A/H3N2, B/Yamagata and B Victoria), in terms of ratio of GMTs and % of subjects who achieve a HI titre of ≥1:40, in subjects ≥6 to <72 months of age.
- To compare the HI antibody response to aQIV and TIV/QIV of healthy subjects vs. subjects at high risk 3 weeks after the last vaccination in subjects ≥6 to <72 months of age.

Outcomes/endpoints

Primary efficacy endpoint: The primary measure of efficacy was the estimate of rVE of aQIV relative to non-adjuvanted comparator for preventing first-occurrence RT-PCR-confirmed influenza disease caused by influenza strains related to those contained in aQIV and non-adjuvanted comparator in children ≥6 to <72 months of age, for ILI cases occurring at ≥21 days and ≤ 180 days after the last vaccination or until the end of the influenza season, whichever was longer.

For the efficacy objectives, the subject had to fulfil the case definition of influenza disease. Active surveillance for ILI for each subject was conducted via telephone contacts, emails and/or text messages weekly from Day 1 up to 180 days after the last vaccination or until the end of the influenza season, whichever was longer.

The protocol-defined criteria for Influenza like illnesses (ILI) were in accordance to the CDC criteria modified for young children: body temperature of ≥100.0°F / ≥37.8°C along with any of the following: cough, sore throat, nasal congestion, or runny nose.

Subjects who met the protocol definition for ILI had an unscheduled clinic visit in order to have a nasopharyngeal (NP) swab collected for evaluation of the presence of influenza virus. The NP swabs were targeted for collection within 3 days of onset of ILI to ensure optimal viral yield, however samples were accepted if collected up to 6 days following ILI-onset day. Clinical specimens were analysed by RT-PCR. All samples were also cultured for the growth of the clinical strain of influenza obtained from the subjects, allowing for antigenic characterization (to determine whether the clinical isolate is antigenically matched or antigenically unmatched to the vaccine strain). All samples were also cultured for the growth of the clinical strain of influenza obtained from the subjects, including evaluating antigenic characterization. Antigenically matched and unmatched strains were those with a <8 and ⩾8-fold difference in titre as compared to the vaccine strain, respectively.

Samples that were culture-positive, were set for viral expansion. In case the HA titre of the expanded sample was ⩾1:8, the expanded sample was shipped to the laboratory for subsequent antigenic typing by means of HI assays. If the viral expansion resulted in HA titre <1:8, a swab aliquot was shipped to another laboratory. Following the culture of the virus at this laboratory, antigenic typing was performed by means of MN assay for influenza A and by HI assay for influenza B.

The analysis of VE against A/H3N2 influenza antigenically matched to vaccine strains combined the results of the samples tested at both laboratories, one using the HI assay and the other the MN assay. There was no A/H3N2 sample which was tested in both laboratories at this stage. After unblinding, the results from the 2 labs resulted to be totally opposite: according to the lab using the HI assay, 7.5% of the cases were unmatched, whereas 98.5% were unmatched when tested at the lab using the MN assay. Apparently, the reason for this discrepant result was due to the HA antigen used to generate the ferret antiserum used in the assays. This HA antigen used by the two laboratories had differences in their amino acid sequence being the one used by the lab using the HI assay more similar to a cell-based virus whereas the one used by the lab using the MN assay being the egg based virus. Thus, all the samples tested initially at the lab using the HI assay were retested at the lab using the MN assay, and then 87.5%

of them were found to be unmatched. This result was in agreement with epidemiological data of H3 viruses isolated during that season. The Company then concluded that considering the antigenic difference between the cell-derived A/H3N2 strain, used in the lab using the HI assay to generate the ferret antiserum, and the egg-derived vaccine strain, the results obtained by the lab using the MN assay are the one that more accurately reflect antigenic matching of the influenza cases detected in study V118_05. These are the results described in the application.

The applicant did not retest A/H1N1, B/Yamagata and B/Victoria strains at the lab using the MN assay for the following reasons:

- WHO recommendations to use MN assay for antigenic characterisation were limited to A/H3N2 strains only;
- The majority of circulating A/H1N1 and B clinical isolates have sufficient hemagglutination titre and could therefore be tested using HI assay;
- There was no egg-adaptation for A/H1N1 and B strains described during the NH 2014/15 season that would lead to modification of antigenicity;
- The results of antigenic characterisation for circulating A/H1N1 and B strains were consistent with available epidemiological data (Appiah 2015; Hammond 2015).

Secondary efficacy endpoints:

The RT-PCR case definition and culture-confirmed case definition was used for secondary efficacy objectives. Endpoints evaluated in all subjects in the age groups ≥6 to <72 months of age, ≥6 to <24 months of age, ≥6 to <36 months of age and ≥36 to <72 months of age were:

- on first-occurrence of RT-PCR-confirmed influenza cases on first-occurrence of RT-PCR-confirmed influenza cases ≥7 days after the last vaccination up to ≤ 180 days after the last vaccination or until the end of the influenza season, whichever was longer in all subjects.

Immunogenicity endpoints

Relevant endpoints for immunogenicity measured in aQIV and non-adjuvanted comparator as determined by HI included:

- GMTs in vaccine naïve and non-naïve subjects on the different time points (D1, D22/50, D181) and GMRs (after vaccination/before vaccination) of HI in these populations.
- Ratio of HI GMT of aQIV vs comparator in vaccine naïve and non-naïve subjects at different timepoints.
- Seroconversion rates at different time points (D1, D22/50, and D181) in vaccine naïve and non-naïve subjects and in those who received aQIV vs TIV/QIV.
- Differences of HI antibody response to aQIV and comparator vaccines in healthy subjects vs subjects with high risk 3 weeks after the last vaccination.

Endpoints were assessed for homologous strains in PPS Immunogenicity and FAS Immunogenicity and for non-matching (heterologous) strains in FAS Immunogenicity Heterologous. In addition, immunogenicity results for two homologous strains measured by microneutralisation (MN) assay were reported for a subset of 600 subjects.

Sample size

Assuming a relative vaccine efficacy of 36% and an event rate (ER) of influenza of 2.50% in the non-adjuvanted comparator arm (Fluzone TIV in a first influenza season and Fluzone QIV in a second

season and possible subsequent seasons) and therefore 1.62% in the aQIV arm, the sample size of approximately 8,124 evaluable subjects aged ≥6 months to<72 months of age for the aQIV arm and 8,124 for the non-adjuvanted comparator arm and with that a number of 323 influenza events predicts ca. 97.5% power for the adjusted 2.02% level one-sided log-rank test for equality of survival curves to detect the difference between the two groups.

Assuming a drop-out rate of 15% percent, approximately 9,558 subjects should be enrolled for each vaccine group (aQIV and non-adjuvanted comparator).

Randomisation

Enrolled subjects were randomly assigned to one of 2 study groups (aQIV or non-adjuvanted comparator) in a prespecified ratio of 1:1 with stratification factors as study site, age group (≥6 to <36 months of age/ ≥36 to <72 months of age, ratio 1:1), vaccine status (naïve/ non-naïve) and for presence of high risk medical condition (at risk/not at risk). All subjects enrolled in the first season were enrolled into the immunogenicity subset. In the second season, of the first approximately 4,000 enrolled subjects, a subset of 1,424, healthy subjects and 356 subjects at high risk were randomized into the immunogenicity subset at a 1:1 ratio to aQIV or non-adjuvanted comparator respectively with the stratification factors country, age group (≥6 to <36 months of age/ ≥36 to <72 months of age, ratio 1:1) and vaccine status (naïve/ non- naïve).

Blinding (masking)

The trial was designed as an observer-blind study. Neither the subject nor any of the investigator staff who were involved in the treatments or clinical evaluation of the subject was aware of the vaccine administered. Only the designated nurse or physician who is responsible for administering the study vaccines was unblinded.

Investigators, sponsor study team, all laboratory personnel involved in processing samples and performing immunogenicity or swab sample assays and others who were involved in the conduct of the study or in the analysis of the final study results, or who had contact with study sites, were to remain blinded to the treatment codes and interim analysis results (if applicable) until all monitoring decisions had been made by the DMC and the database had been locked for final analysis.

Statistical methods

Study Analysis Population Sets

- All Enrolled Set

All screened subjects who provided informed consent and provided demographic and/or other baseline screening measurements, were randomized and received a subject ID.

- Exposed Set

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

- Full Analysis Set (FAS) Efficacy/Immunogenicity

Primary and Secondary Efficacy Objectives

FAS Efficacy: All subjects in the Enrolled Set who actually received a study vaccination and were evaluated for efficacy at least 21 days after the last vaccination.

Secondary Immunogenicity Objectives

FAS Immunogenicity: All subjects in the Enrolled Set selected for Immunogenicity Subset during randomization, who received a study vaccination AND provided evaluable serum samples for both before (baseline) and after vaccination.

Based on type of immunogenicity assay performed on the serum samples, the following FAS immunogenicity Sets were defined:

- FAS immunogenicity Homologous (further referred to simply as "FAS Immunogenicity Set"),
- FAS Immunogenicity Heterologous.

- *Early Efficacy Objectives*

FAS Early Efficacy: All subjects in the Enrolled Set who actually received a study vaccination and were evaluated for efficacy at least 7 days after the last vaccination.

- *Exploratory Efficacy and Immunogenicity Objectives*

FAS Immunogenicity Microneutralization (MN): All subjects in the Enrolled Set who received a study vaccination AND provided evaluable serum samples for MN analysis for both before (baseline) and after vaccination.

Exploratory efficacy or immunogenicity objectives were only evaluated for the FAS (FAS Efficacy / FAS Immunogenicity MN).

- *Modified Full Analysis Set (MFAS) Efficacy*

All subjects in the FAS Efficacy who received exclusively study vaccination. Subjects who received an additional non-study influenza vaccine prior to 180 days after last study vaccination or the end of the influenza season, whichever was longer, were excluded from this analysis set.

The MFAS is provided for sensitivity analyses to provide evidence of the robustness of the primary analysis.

- *Per Protocol Set (PPS) Efficacy/Immunogenicity*

The PPS included all subjects or data points of subjects in the FAS Efficacy/Immunogenicity which were not excluded due to reasons defined prior to unblinding or analysis defined prior to unblinding or analysis.

Primary Efficacy Analysis

The HR and the related 95% confidence interval (CI), for onset of RT-PCR confirmed influenza was estimated by a Cox proportional hazards regression model with treatment effect as a fixed effect and the stratification factors (country, age cohort, vaccine status and presence of high risk medical condition) as well as Season considered as random effect. Instead of the stratification factor centre, the factor country was used in the model.

The study is successful if the upper-limit (UL) of the two-sided 95% confidence interval of the hazard ratio is lower than 1, or equivalently if the lower-limit (LL) of the two-sided 95% confidence interval of the relative vaccine efficacy, rVE, is above 0.

The Efficacy FAS population will be used for the primary efficacy analysis.

Secondary Immunogenicity Analyses

For each strain and time point, the logarithmically (base 10) transformed titre values were analysed using an analysis of covariance with the factors vaccination group, age, naivety, health status, season and with covariable the logarithmically transformed baseline.

The applicant considered missing immunogenicity values as MCAR's.

Multiplicity

No a-priori confirmation strategy or multiplicity correction was defined. This means that, except for the primary analyses, all other analyses, including subgroup analyses, will be considered explorative.

Results

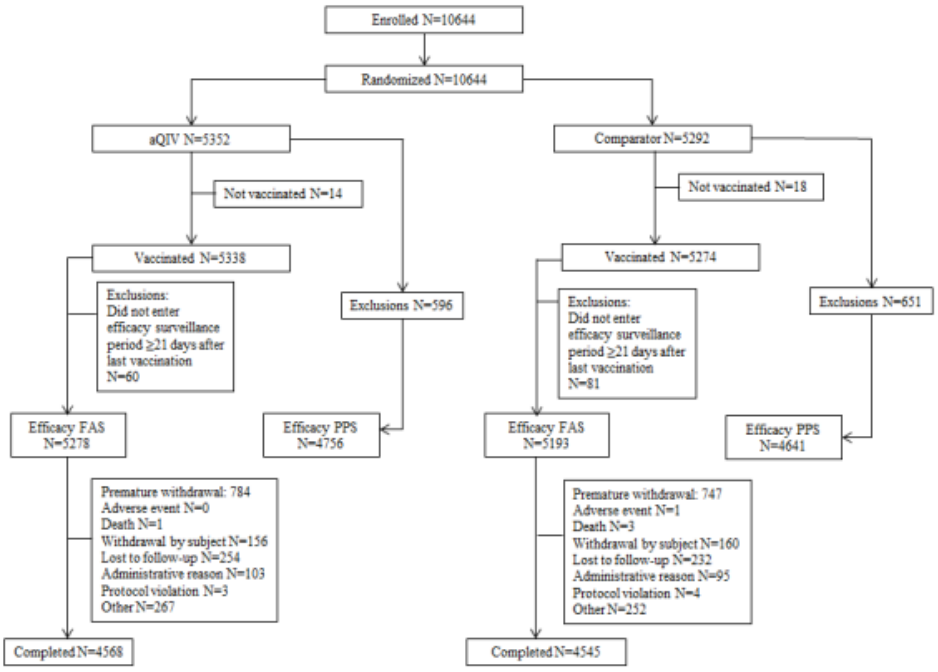
Participant flow

Overall, 10,644 subjects ≥6 to <72 months of age were enrolled/randomized to receive aQIV or comparator vaccine (Fluzone TIV in Season 1 and Fluzone QIV in Season 2) in a 1:1 ratio. Of these, 5,352 subjects were enrolled in the aQIV group and 5,292 subjects in the comparator vaccine group. Of these, 10,612 were vaccinated, 5,338 (99.5%) subjects in the aQIV group and 5,274 (99.5%) subjects in the comparator vaccine.

Study Participant flow

Subject completion flowchart is provided in Figure 1 for the Efficacy Set.

Figure 1 Participant flow for the efficacy set



Source: Table 14.1.1.1, Table 14.1.1.8.1, Table 14.1.1.2.1
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; N=number of subjects. Exclusions from PPS (596 for aQIV and 651 for comparator are detailed in Section 10.2).
The number of premature withdrawals is derived from the number of subjects randomized.

Of the 10,644 enrolled subjects, 9,113 (85.6%) subjects completed the study. A total of 4,568 (85.4%) to 4,545 (85.9%) of subjects across vaccine groups completed the study with the same proportion of early terminations between the 2 vaccine groups. The reasons for termination were similar between the

vaccine groups. Across both vaccine groups, the most common reasons for early terminations were lost to follow-up (486 [4.6%] subjects) and enrollment in the V118_05E1 study (461 [4.3%] subjects). V118_05E1 was the revaccination study in which some of the subjects enrolled in Season 1 of the current V118_05 study could be enrolled to receive another vaccination in the next influenza season.

A similar analyses was performed according to stratification by age (aged ≥6 to <36 months and ≥36 to <72 months) or by season. In both cases, no significant asymmetry was observed for the several parameters analysed.

Exclusions from Efficacy Population

There were no notable differences in the proportion of subjects excluded from the PPS Efficacy Set between the aQIV and comparator vaccine groups.

Overall, 1,247 subjects (11.7%) in the All Enrolled Set were excluded from the PPS Efficacy population. The proportion of subjects excluded from the PPS Efficacy population was similar between the vaccine groups (11.1% in aQIV and 12.3% in comparator vaccine groups). The main reasons for exclusion were second vaccination performed out of window (4.5%) and second vaccination not done (3.0%).

Recruitment

A total of 1,486 subjects were enrolled in Season 1 and 9,158 in Season 2. Subjects were enrolled in the following countries in Season 1: Canada (N=90 [6.2%]), Finland (N=150 [10.3%]) and United States of America (N=1216 [83.5%]). Subjects were enrolled in the following countries in Season 2: Canada (N=90 [1.0%] subjects), Finland (N=492 [5.5%] subjects), Italy (N=206 [2.3%] subjects), The Philippines (N=2270 [25.2%] subjects), Poland (N=440 [4.9%] subjects), Spain (N=49 [0.5%] subjects), Taiwan (N=280 [3.1%] subjects), Thailand (N=2028 [22.5%] subjects), and United States of America (N=3160 [35.1%] subjects).

Subjects were enrolled in Season 1 from November 2013- January 2014 and in Season 2 from September 2014 -January 2015 (NH countries: Season 2a) and January- March 2015 (Tropical countries: Thailand and Philippines: Season 2b). Active surveillance for ILI was conducted from Day 1 to 180 days after last vaccination or the end the influenza season, whichever is longer. The end of June (NH countries) or end of October (Thailand and Philippines) was defined as the end of influenza season.

Conduct of the study

Protocol amendments

There were 5 amendments to the original protocol (dated 28 March 2013). No subjects were treated under the original protocol and Protocol Amendment 1. At the time of first subject first visit (FSFV), 03 Nov 2013, Protocol Amendment 2 (Protocol Version 3.0) was in place. There were no key non-editorial changes from Protocol Amendment 3 (dated 06 Jun 2014) and Protocol Amendment 5 (dated 28 Sep 2015).

Out-of-Specification and Use of Commercial Vaccine in Season 1

During the conduct of Season 1, the 5-month stability test on the supplied aQIV batch demonstrated that the HA content measured by single radial immunodiffusion (SRID) assay for aQIV was below the specification of 27 µg HA/mL for 3 out of 4 of the influenza strains included in the vaccine. Both influenza B strains and A/H1N1 were below the specification. The A/H3N2 HA content was well within specification. As a result of the out-of-specification observation, enrollment was stopped on 29 Jan 2014. In addition, it was decided to hold administration of the second vaccine dose intended for naïve subjects. At the time

of the Sponsor's decision to stop enrollment, 1486 children ≥6 to <72 months of age had been enrolled with 1481 subjects exposed to at least one study vaccination.

The majority (N=88%) of vaccine naïve subjects received a second dose of study vaccine in Season 1. From the 124 vaccine naïve subjects not receiving a second vaccination, 65 subjects did not receive a second vaccination because of the out-of-specification and 59 subjects did not receive a second vaccination because of another reason. In view of the time required to obtain the reconsent of the parents after the hold, there was a delay in the administration of second vaccinations in 149 vaccine naïve subjects (range Day 37-91, median Day 43). The last study vaccinations in Season 1 were administered on March 5, 2014. Subjects vaccinated out of window were included in the FAS but excluded from PPS Efficacy and immunogenicity analyses.

Since a decrease in HA content would potentially reduce the immunogenicity of the vaccine, inclusion of these results in the overall analysis would tend to bias towards a conservative estimation of immune response or efficacy for aQIV as compared to the nonadjuvanted influenza vaccine. Moreover, in view of the relatively small portion of subjects enrolled during Season 1, i.e., approximately 14% of the overall number of enrolled subjects in the study, the potential impact on the overall efficacy data was estimated to be minimal.

Baseline data

Summary of the demographic and other baseline characteristics for the All Enrolled Set overall is presented in

Table 7.

The total enrolled population comprised of predominately Asian (44.2%) and White (39.9%) subjects. In relation to age baseline, 47.3% in the ≥6 to <36 months age group, 52.7% in the ≥36 to <72 months age group, 25.2% of the subjects were in the ≥6 to <24 months age group and 74.8% in ≥24 to <72 months age group. Overall, the proportion of males and females was similar (50.8% vs. 49.2%, respectively). There were more vaccine-naïve than vaccine non-naïve subjects enrolled in the study (67.7% vs. 32.3%, respectively). There were more subjects enrolled in Season 2 than in Season 1 (86.0% vs. 14.0%, respectively). The majority of subjects were healthy (91.3%) and 8.7% of the subjects were considered to be at high risk of influenza complications. Protocol criteria for inclusion were met for 98.8% of subjects. Subjects in the aQIV and comparator vaccine groups were well balanced with respect to mean age, as well as with respect to vaccine naivety status, race, sex, ethnic origin and risk factor.

Table 6: **Demographic and baseline characteristics in subjects ≥6 to <72 months of age – all enrolled set**

	aQIV N=5352	Comparator[a] N=5292	Total N=10644
Age (months) Mean, SD:	38.4, 18.43	38.0, 18.40	38.2, 18.42
Age Group(n[%]):			
≥6 to <24 Months	1322 (24.7)	1364 (25.8)	2686 (25.2)
≥24 to <72 months	4030 (75.3)	3928 (74.2)	7958 (74.8)
≥6 to <36 Months	2519 (47.1)	2516 (47.5)	5035 (47.3)
≥36 to <72 Months	2833 (52.9)	2776 (52.5)	5609 (52.7)
Sex (n[%]):			
Male	2709 (50.6)	2702 (51.1)	5411 (50.8)
Female	2643 (49.4)	2590 (48.9)	5233 (49.2)
Race (n[%]):			
American Indian or Alaska Native	10 (0.2)	11 (0.2)	21 (0.2)
Asian	2348 (43.9)	2361 (44.6)	4709 (44.2)
Black or African American	711 (13.3)	692 (13.1)	1403 (13.2)
Native Hawaiian or other Pacific Islander	14 (0.3)	16 (0.3)	30 (0.3)
White	2153 (40.2)	2091 (39.5)	4244 (39.9)
Other	116 (2.2)	121 (2.3)	237 (2.2)
Naïvety Status (n[%]):			
Vaccine Naïve	3611 (67.5)	3597 (68.0)	7202 (67.7)
Vaccine Non-naïve	1741 (32.5)	1695 (32.0)	3436 (32.3)
Health status (n[%]):			
Healthy	4879 (91.2)	4838 (91.4)	9717 (91.3)
At High Risk	473 (8.8)	454 (8.6)	927 (8.7)
Season 1 (n[%]):	773 (14.4)	713 (13.5)	1486 (14.0)
Season 2 (n[%]):	4579 (85.6)	4579 (86.5)	9158 (86.0)
Met Protocol Criteria (n[%]):			
No	62 (1.2)	62 (1.2)	124 (1.2)
Yes	5290 (98.8)	5230 (98.8)	10520 (98.8)

Source: Table 14.1.1.3

Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; n=number of values in category; N=total number of subjects; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine; SD=standard deviation.

[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

Vaccine naïve (not previously vaccinated) subjects were defined as subjects that had not received 2 or more doses of seasonal influenza vaccine since July 1, 2010 or who did not know their influenza vaccination history.

Vaccine non-naïve: subjects who had been previously vaccinated and received 2 or more doses of seasonal influenza vaccine since July 1, 2010.

Numbers analysed

Efficacy Data Sets

A total of 1,0644 subjects were enrolled (randomized) into the study. Of those enrolled, 10,471 (98.4%) subjects were included in the FAS analysis for the primary efficacy objective. The overview of efficacy data sets analysed in subjects ≥6 to <72 months of age – as randomised is included in the Table below.

Table 7: Overview of efficacy data sets analysed in subjects ≥6 to <72 months of age – as randomised

	aQIV N=5352 n (%)	Comparator[a] N=5292 n (%)	Total N=10644 n (%)
All Enrolled Set	5352 (100.0)	5292 (100.0)	10644 (100.0)
All Exposed Set	5338 (99.7)	5274 (99.7)	10612 (99.7)
FAS – Efficacy Objectives			
FAS	5278 (98.6)	5193 (98.1)	10471 (98.4)
MFAS	5240 (97.9)	5169 (97.7)	10409 (97.8)
Early Efficacy FAS	5286 (98.8)	5208 (98.4)	10494 (98.6)
PPS – Efficacy Objectives			
PPS	4756 (88.9)	4641 (87.7)	9397 (88.3)
FAS Health Economics	255 (4.8)	250 (4.7)	505 (4.7)

Source: Table 14.1.1.1
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; FAS=full analysis set; MFAS=modified full analysis set; PPS=per protocol set; n=number of values in category; N=total number of subjects; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine.
[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

Immunogenicity Data Sets

The overview of immunogenicity data sets analysed in subjects ≥6 to <72 months of age – as randomised is presented in the Table below.

Table 8: Overview of efficacy data sets analysed in subjects ≥6 to <72 months of age – as randomised

	aQIV N=5352 n (%)	Comparator[a] N=5292 n (%)	Total N=10644 n (%)
All Enrolled set	5352 (100.0)	5292 (100.0)	10644 (100.0)
Enrolled Immunogenicity	1662 (31.1)	1594 (30.1)	3256 (30.6)
All Exposed Set	5338 (99.7)	5274 (99.7)	10612 (99.7)
FAS – Immunogenicity			
FAS Immunogenicity	1481 (89.1)*	1405 (88.1)*	2886 (88.6)*
FAS Immunogenicity Heterologous	297 (17.9)*	295 (18.5)*	592 (18.2)*
PPS – Immunogenicity			
PPS Immunogenicity	1244 (74.8)*	1174 (73.7)*	2418 (74.3)*
PPS Immunogenicity Heterologous	252 (15.2)*	248 (15.6)*	500 (15.4)*

Source: Table 14.1.1.1.5
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; FAS=full analysis set; PPS=per protocol set; n=number of values in category; N=total number of subjects.
[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.
Note: Enrolled refers to randomized subjects
* Percentage is based on number of subjects enrolled in the Immunogenicity Set.

Outcomes

Analysis of Efficacy

For any subject who had multiple confirmed influenza infections, only the first occurrence confirmation was counted under ANY strain. However, for all confirmed influenza infections, the first-occurrence for each strain was counted separately under each respective individual confirmed strain.

There were 5 subjects who had a culture-confirmed influenza although the original swab material tested RT-PCR negative for the influenza strain. All 5 swabs were collected via the NP route within a few days from ILI-onset. All were first-occurrence cases.

Primary Efficacy Analysis

A total of 508 first-occurrence influenza cases were confirmed by RT-PCR (256 (4.9%) in the aQIV arm and 252 (4.9%) in the comparator arm).

The criterion for demonstrating a difference in rVE between aQIV and the comparator vaccine group was not met in subjects ≥6 to <72 months of age in the FAS, since the pre-specified statistical criterion (LL of the 2-sided 95% CI for the rVE >0%) of the rVE estimate was <0 (rVE -0.67 [95% CI: -19.81; 15.41]).

Similarly, the criterion for demonstrating a difference in rVE between aQIV group and the comparator vaccine group was not met in subjects ≥6 to <72 months of age in the PPS (rVE -0.02 [95% CI: -20.07; 16.68]). The PPS data confirmed FAS output and robustness of data.

Table 9: Number of subjects with first-occurrence RT-PCR-confirmed influenza and relative vaccine efficacy (95% CI) in subjects ≥6 to <72 months of age for all seasons – FAS efficacy

	aQIV N=5278	Comparator[a] N=5193	rVE (95%CI)
Number of cases (attack rate)- any strain[b]	256 (4.9%)	252 (4.9%)	-0.67 (-19.81; 15.41)

Source: Table 14.2.1.1.1

Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; FAS=full analysis set; rVE=relative vaccine efficacy; reaction; N=total number of subjects; PCR=PCR=polymerase chain reaction; RT-PCR=reverse transcriptase polymerase chain; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine.

[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

[b] Any strain=any strain regardless of antigenic match.

B/Victoria cases from Season 1 have not been included in the analysis.

rVE (vaccination efficacy)=(1- the hazard rate of treatment/hazard rate of comparator)x100%; Attack rate=(cases/N)x100%. The 95% CI of attack rate is based on Clopper-Pearson's method.

Result is based on the Cox proportional hazards model for time until onset of the first PCR-confirmed influenza occurring at ≥21 days and ≤180 days after last vaccination or until the end of the season, whichever was longer with vaccine group as the main effect, adjusting for vaccine naïvety, risk factor, season, age group and country as random effects.

Secondary Efficacy Analysis

Relative Vaccine Efficacy: RT-PCR-Confirmed Influenza by Strain

A total of 24 A/H1N1, 396 A/H3N2, 72 B/Yamagata and 23 B/Victoria first-occurrence influenza cases were confirmed by RT-PCR. aQIV had better rVE than comparator vaccine against the RT-PCR-confirmed A/H1N1 strain; rVE 59.39 (95% CI: 2.06; 83.16). No difference in rVE between aQIV and comparator was demonstrated for the RT-PCR-confirmed A/H3N2 and B strains in subjects ≥6 to <72 months of age.

Table 10: Number of subjects with first-occurrence RT-PCR-confirmed influenza and relative vaccine efficacy (95% CI) by strain in subjects ≥6 to <72 months of age for all seasons – FAS efficacy

Strain[b]	aQIV N=5278	Comparator[a] N=5193	rVE (95%CI)
Number of cases (attack rate)- any strain[c]			
A/H1N1	7 (0.1%)	17 (0.3%)	59.39 (2.06; 83.16)
A/H3N2	200 (3.8%)	196 (3.8%)	-1.33 (-23.41; 16.79)
B/Yamagata	36 (0.7%)	36 (0.7%)	2.09 (-55.44 ; 38.33)
B/Victoria[d]	14 (0.3%)	9 (0.2%)	-54.47 (-256.90; 33.14)

Source: Table 14.2.1.1.2, Table 14.2.1.1.3, Table 14.2.1.1.4 and Table 14.2.1.1.5

Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; FAS=full analysis set; N=total number of subjects in group; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine; RT-PCR=reverse transcriptase polymerase chain reaction; rVE=relative vaccine efficacy.

[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

[b] A/H1N1=A/California/7/2009 pdm09-like virus, A/H3N2=A/Texas/50/2012, B/Yamagata=B/Massachusetts/2/2012 and B/Victoria=B/Brisbane/60/2008.

[c] Any strain=any strain regardless of antigenic match.

[d] B/Victoria cases from Season 1 have not been included in the analysis (N=4521 for aQIV, N=4494 for comparator).

Relative Vaccine Efficacy: Culture-Confirmed Influenza

A total of 286 subjects experienced at least 1 case of first-occurrence influenza which was confirmed by culture. No difference in rVE between aQIV and comparator was demonstrated for any strain or the matched and unmatched culture-confirmed A and B strains in subjects ≥6 to <72 months of age.

Post-hoc analysis of *Relative Vaccine Efficacy: Culture-Confirmed Influenza*

Study V118_05 had the majority of cases in the 2014-15 season, which was known to be a mismatched season for A/H3N2 (i.e., the strain that was circulating in the season was antigenically distinct from the vaccine strain). Upon evaluation of the data, there appeared to be a discrepancy between the percentages of antigenically matched cases for the A/H3N2 strain in this study versus the influenza epidemiology from the season in which the majority of cases were obtained.

As described in detail above, firstly, samples were antigenically typed by a laboratory using a hemagglutination inhibition (HI) assay and if no result could be obtained the samples were typed by another lab using a microneutralization (MN) ViroSpot. According to the lab using the HI assay, a significantly greater fraction of cases reported to be matched compared to the seasonal epidemiology results. Samples initially tested by the lab using the HI assay were therefore retested by the other lab using the same MN ViroSpot assay. The results of this additional analysis is shown in the next Table. The values in italics indicate new data from the post-hoc analysis, including supplemental typing results for A/H3N2 vaccine strain.

Table 11: Number of subjects with cultured-confirmed influenza (overall, antigenically matched and unmatched strains) and relative vaccine efficacy (95% CI) in subjects ⩾6 to <72 months of age for all seasons – FAS efficacy

Strain[b]	aQIV N = 5278	Comparator[a] N = 5193	rVE (95%CI)
Number of cases (attack rate) – any strain[c]	**140 (2.7)**	**146 (2.8)**	**5.21 (-19.53; 24.83)**
A/H1N1	5 (0.1)	9 (0.2)	NA
A/H3N2	96 (1.8)	104 (2.0)	8.60 (-20.62; 30.75)
B/Yamagata	29 (0.6)	27 (0.5)	-5.56 (-78.32; 37.52)
B/Victoria[d]	10 (0.2)	8 (0.2)	NA
Number of cases (attack rate) - matched strain[e]	***39 (0.7)***	***43 (0.8)***	***10.42 (-38.19; 41.93)***
A/H1N1	5 (0.1)	8 (0.2)	NA
A/H3N2	*4 (0.1)*	*6 (0.1)*	*34.15 (-133.35; 81.42)*
B/Yamagata	21 (0.4)	23 (0.4)	10.01 (-62.60; 50.20)
B/Victoria[d]	9 (0.2)	6 (0.1)	NA
Number of cases (attack rate) - unmatched strain[e]	***94 (1.8)***	***93 (1.8)***	***-0.15 (-33.40; 24.82)***
A/H1N1	0	0	NA
A/H3N2	*85 (1.6)*	*87 (1.7)*	*3.14 (-30.61; 28.17)*
B/Yamagata	8 (0.2)	4 (0.1)	NA
B/Victoria[d]	1 (0.0)	2 (0.0)	NA

Source: Table 14.2.1.2.1, Table 14.2.1.2.1.1, Table 14.2.1.2.1.2, Table 14.2.1.2.1.3, Table 14.2.1.2.1.4, Table 14.2.1.3.1.99, Table 14.2.1.3.1.1, Table 14.2.1.3.1.2.99, Table 14.2.1.3.1.3, Table 14.2.1.3.1.4, Table 14.2.1.4.1.99, Table 14.2.1.4.1.1, Table 14.2.1.4.1.2.99, Table 14.2.1.4.1.3 and Table 14.2.1.4.1.4.

Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; FAS=full analysis set; N=total number of subjects; The actual number of results may vary by time point and strain; NA=not applicable; QIV=quadrivalent influenza vaccine; rVE=relative vaccine efficacy; SAP=statistical analysis plan; TIV=trivalent influenza vaccine.

[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

[b] A/H1N1=A/California/7/2009 pdm09-like virus, A/H3N2=A/Texas/50/2012, B/ Yamagata=B/Massachusetts/2/2012 and B/Victoria=B/Brisbane/60/2008.

[c] Any strain=any strain regardless of antigenic match.

[d] B/Victoria cases from Season 1 have not been included in the analysis.

[e] Matched strains are those with a <8-fold difference in titer and unmatched strains are those with ≥8-fold difference in titer compared with the vaccine strain.

For culture-confirmed influenza: Subjects 2012094 and 2072011 (both comparator vaccine group) had a first-occurrence infection with A/H3N2 and a later infection with B/Yamagata.

NA: Per SAP, the rVE was not calculated if number of cases was <20.

rVE(vaccination efficacy) = (1- the hazard rate of treatment/hazard rate of Comparator)x100%; Attack rate = (cases/N)x100%. The 95% confidence interval of attack rate is based on Clopper-Pearson's method.

Result is based on the Cox proportional hazards model for time until onset of the first culture-confirmed influenza occurring at ≥21 days and ≤180 days after last vaccination or until the end of the season, whichever was longer with vaccine group as the main effect, adjusting for vaccine naïvety, risk factor, season, age group and country as random effects.

From this post hoc analysis it can be seen that:

- The vast majority of A/H3N2 influenza cases after re-analysis were determined to be unmatched to the vaccine strain; 4 cases in aQIV and 6 cases in comparator group were reported as matched A/H3N2 cases in the supplemental analysis.
- Upon the supplemental A/H3N2 antigenic typing, the number of matched cases decreased and the number of unmatched cases increased. The decrease in the number of matched cases resulted in wider 95% confidence intervals for the vaccine group comparisons.
- The conclusions from the original data (CSR dated 22 June 2017) with regards to rVE for culture confirmed matched and unmatched strains remain unaltered, i.e., there was no difference in relative efficacy between aQIV and comparator vaccine for culture-confirmed matched or unmatched influenza strains in subjects ≥6 to <72 months of age.

As discussed earlier, the data in the Table above are the ones that reflect the real situation of trial V118_05 since it was found that the laboratory using the HI assay used an inadequate reagent for antigenically characterizing the H3N2 influenza cases.

Relative Vaccine Efficacy by Age.

RT-PCR-Confirmed Influenza by Age.

The rVE was 4.03 (95% CI: -24.02; 25.74) for ≥6 to <36 months age group, -4.88 (95% CI: - 32.94; 17.26) for ≥36 to <72 months age group and -14.99 (95% CI: -40.93; 6.18) for ≥24 to <72 months age group.

However, in the ≥6 to <24 months age group, the LL of the 2-sided 95% CI was >0 and rVE estimate for any RT-PCR-confirmed strain was 31.37 (95% CI: 3.14; 51.38). No statistically significant difference in vaccine efficacy was observed in >24 to <72 months.

The relative vaccine efficacy by age subgroup (≥6 to <12 months, ≥12 to <24 months, and ≥24 to <36 months) is presented in the table below. The rVE of aQIV is similar in subjects 6 to <12 months and ≥12 to <24 months of age were 35.73% and 28.83%, respectively). None of these rVE estimates were statistically significant.

Table 12: relative vaccine efficacy (rVE) against any PCR-confirmed influenza of aQIV vs the comparator vaccine, by age category – FAS Efficacy

Age group	Number of subjects		Number of PCR-confirmed influenza cases (attack rate)		Adjusted rVE (95% CI)
	aQIV	Comparator	aQIV	Comparator	
≥6 to <12 months	432	450	18 (4.2%)	28 (6.2%)	35.73 (-16.25, 64.47)
≥12 to <24 months	867	889	37 (4.3%)	51 (5.7%)	28.83 (-8.73, 53.42)
≥24 to <36 months	1185	1132	60 (5.1%)	40 (3.5%)	-49.08 (-122.53, 0.13)

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; PCR-confirmed = Polymerase chain reaction-confirmed; rVE=relative Vaccine Efficacy; CI= Confidence Interval.
Source: V118_05 Table q102-cr73-cr76-v11805-14-2-1-1-6

The estimated adjusted rVE against any PCR-confirmed influenza and influenza attack rates in each study group for vaccine-naïve and non-vaccine-naïve subjects ≥6 to <24 months and ≥24 to <72 months of age is presented below (see Table 14).

The majority of subjects (1,130 of 1,299; 87%) in age group ≥6 to <24 months were vaccine-naïve. The rVE in the vaccine naïve subjects ≥6 to <24 months was 34.08% (95% CI: 5.28, 54.12). The rVE of vaccine non-naïve children in this age group was -0.88% (95% CI: -212.80, 67.46).

There was no difference in rVE of aQIV in vaccine-naïve and vaccine non-naïve subjects ≥24 to <72 months (-15.19% and -15.03%, respectively). The ≥24 to <72 months age subgroup included a lower proportion of vaccine naïve subjects relative to the younger age subgroup (61% vaccine naïve and 39% vaccine non-naïve). Additionally, with an influenza annual attack rate of 10% to 30% in children <6 years (Bodewes 2011; Jayasundara 2014) it is expected that a substantial proportion of subjects in this age group will be serologically non-naïve, regardless of influenza vaccination history.

Table 13: relative vaccine efficacy (rVE) against any PCR-confirmed influenza of aQIV vs the comparator vaccine, by age category and vaccine-naivety status – FAS Efficacy

Group	Number of subjects		Number of PCR-confirmed influenza cases (attack rate)		Adjusted rVE (95% CI)
	aQIV	Comparator	aQIV	Comparator	
≥6 to <24 months: vaccine-naïve	1130	1167	49 (4.3%)	73 (6.3%)	34.08 (5.29, 54.12)
≥6 to <24 months: vaccine non-naive	169	172	6 (3.6%)	6 (3.5%)	-0.88 (-212.80, 67.46)
≥24 to <72 months: vaccine-naïve	2423	2358	111 (4.6%)	97 (4.1%)	-14.68 (-50.61, 12.68)
≥24 to <72 months: vaccine non-naive	1556	1496	90 (5.8%)	76 (5.1%)	-14.33 (-55.20, 15.78)

Culture-Confirmed Influenza by Age

No significant differences were observed in any of the age groups including 6 to 24 when the data from cell-culture confirmed cases were analyzed.

Relative Vaccine Efficacy by Prior Vaccination Status and by season

No statistically significant results were obtained in these subgroups when the rVE was calculated using either RT-PCR or cell culture confirmed influenza cases.

Relative vaccine efficacy by sex

As shown in Table below, rVE of aQIV compared with comparator vaccine, was greater in males than females. The rVE estimates were statistically superior in both cases since excluded zero. However, the immunogenicity data do not show a similar pattern, since similar GMT titers were reached in males and females within each of the two arms.

Table 14: Number of subjects with first occurrence RT-PCR-confirmed influenza and relative vaccine efficacy (95% CI) in subjects ⩾6 to <72 months of age by sex for all seasons – FAS efficacy

	Males			Females		
	aQIV	Comparator[a]	rVE (95%CI)	aQIV	Comparator[a]	rVE (95%CI)
Strain[b]	N=2709	N=2702		N=2643	N=2590	
Number of cases- any strain[c]	**111**	**146**	**23.89 (2.56; 40.55)**	**145**	**106**	**-34.72 (-73.15; -4.83)**
A/H1N1	2	7	NA	5	10	NA
A/H3N2	87	116	24.27 (-0.03; 42.66)	113	80	-38.75 (-84.84; -4.15)
B/Yamagata	16	22	27.70 (-37.68; 62.03)	20	14	-40.43 (-178.50; 29.19)
B/Victoria[d]	7	5	NA	7	4	NA

Source: Table 14.1.1.3, Table 14.2.1.1.41, Table 14.2.1.1.42, Table 14.2.1.1.43, Table 14.2.1.1.44 and Table 14.2.1.1.45

Early Efficacy

The vaccine efficacy was additionally evaluated before the start of the efficacy period for the primary objective (≥21 days to <180 days after last vaccination). In vaccine naïve subjects, the efficacy of the first vaccine was evaluated ≥7 and ≥14 days after first vaccination until second vaccination.

The rVE was 54.66 (95% CI: 18.08; 74.91) and 70.56 (35.19; 86.62) for ≥7 and ≥14 days after first and up to second vaccination, respectively in vaccine naïve subjects (Table 16) indicating higher early efficacy of the aQIV than the comparator vaccine. In all subjects (pooled naïve and non-naïve), the rVE was 3.70 (95% CI: -14.29; 18.85) ≥7 days and ≤180 days after last vaccination or until end of season, whichever was longer.

Table 15: Number of subjects with first occurrence RT-PCR-confirmed influenza and relative vaccine efficacy (95% CI) in subjects ⩾6 to <72 months of age for all seasons – FAS efficacy

	aQIV	Comparator[a]	rVE (95% CI)
Any strain[b]: vaccine naïve subjects	**N= 3559**	**N=3535**	
≥7 days after first and up to second vaccination	16	35	54.66 (18.08, 74.91)
≥14 days after first and up to second vaccination	8	27	70.56 (35.19,86.62)
Any Strain[b]: all subjects	**N=5286**	**N=5208**	
≥7 days and ≤21 days after last vaccination	4	15	NA
≥7 to ≤180 days after last vaccination or end of season, whichever was longer[b]	259	266	3.70 (-14.29; 18.85)

Source: Table 14.2.1.5.1, Table 14.2.1.5.2, Table 14.2.1.6.1 and Table 14.2.1.7.1
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; FAS=full analysis set; N=total number of subjects; NA=not applicable; PCR=polymerase chain reaction; QIV=quadrivalent influenza vaccine; RT-PCR=reverse transcription polymerase chain reaction; rVE=relative vaccine efficacy; TIV=trivalent influenza vaccine.
[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.
[b] Any strain= any strain regardless of antigenic match.
Per SAP, the rVE was not calculated if number of cases was <20.
rVE (vaccination efficacy)=(1- the hazard rate of treatment/hazard rate of comparator)x100%.
Result is based on the Cox proportional hazards model for time until onset of the first PCR-confirmed influenza with vaccine group as the main effect, adjusting for vaccine naïvety, risk factor, season, age group and country as random effects.

Early Efficacy by Age

The rVE was 63.61 (95% CI: 7.68; 85.66) in the ≥6 to <24 months and 45.23 (95%CI: -18.70; 74.73) in the ≥24 to <72 months age groups against any strain of RT-PCR-confirmed influenza in vaccine naïve subjects ≥7 days after first and up to second vaccination. In the ≥6 to <24 months age group regardless of prior influenza vaccine exposure, the rVE was 34.69 (95% CI: 8.14; 53.57).

Table 16: Number of subjects with first occurrence RT-PCR-confirmed influenza and relative vaccine efficacy (95% CI) in subjects ⩾6 to <24 months and ⩾24 to <72 months for all seasons – FAS efficacy

Table 51: Number of Subjects with First-Occurrence RT-PCR-Confirmed Influenza and Relative Vaccine Efficacy (95% CI) in Subjects ≥6 to <24 months and ≥24 to <72 Months – All Seasons – FAS Early Efficacy

	≥6 to <24 Months			≥24 to <72 Months		
Strain[b]	**aQIV**	**Comparator[a]**	**rVE (95%CI)**	**aQIV**	**Comparator[a]**	**rVE (95%CI)**
Any strain[b]: vaccine naïve subjects	**N=1134**	**N=1170**		**N=2425**	**N=2365**	
≥7 days after first and up to second vaccination	6	17	63.61 (7.68; 85.66)	10	18	45.23 (-18.70; 74.73)
≥14 days after first and up to second vaccination	3	14	NA	5	13	NA
Any strain[b]: All subjects	**N=1303**	**N=1342**		**N=3983**	**N-3866**	
≥7 days and ≤21 days after last vaccination	0	4	NA	4	11	NA
≥7 to ≤180 days after last vaccination	55	83	34.69 (8.14; 53.57)	204	183	-10.03 (-34.35; 9.89)

Source: Table 14.6.5.1, Table 14.6.5.2, Table 14.6.5.3 and Table 14.6.5.4
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; FAS=full analysis set; N=total number of subjects; NA=not applicable; PCR=polymerase chain reaction; QIV=quadrivalent influenza vaccine; RT-PCR=reverse transcription polymerase chain reaction; rVE=relative vaccine efficacy; SAP=statistical analysis plan; TIV=trivalent influenza vaccine.
[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.
[b] Any strain=any strain regardless of antigenic match.
Per SAP, the rVE was not calculated if number of cases was <20.
Both the ≥6 to <24 months and the ≥24 to <72 months age groups were not part of the stratification factors.
The ≥24 to <72 months age group was a posthoc analysis.
rVE (vaccination efficacy)=(1- the hazard rate of treatment/hazard rate of comparator)x100%.
Result is based on the Cox proportional hazards model for time until onset of the first PCR-confirmed influenza with vaccine group as the main effect, adjusting for vaccine naïvety, risk factor, season, age group and country as random effects.

Immunogenicity Analysis

Superiority

The GMTs and percentage of subjects with seroconversion at 21 days after last vaccination are reported for homologous strains in Table 18 and Table 19, respectively for the FAS. The baseline GMTs for all

homologous strains were comparable for the aQIV and comparator groups in subjects ≥6 to <72 months of age. The superiority criteria for GMTs and SC were met for all homologous strains at 21 days following vaccination.

Table 17: Geometric Mean HI titers, geometric mean ratios, GMT ratios and GMT ratios (95% CI) against vaccine strains (superiority) at 21 Days after last vaccination in subjects ≥6 to <72 months of age – all seasons – FAS immunogenicity

Strain[b]	Strains[b]	aQIV N=1481	Comparator[a] N=1405	GMT ratio (95% CI)
		GMT/GMR (95% CI)	GMT/GMR (95% CI)	
A/H1N1	Baseline (Day 1)	40.08 (32.3; 49.7)	39.49 (31.8; 49.1)	
	Day 22/50	996.40 (888.4; 1117.6)	522.50 (465.3; 586.7)	1.91 (**1.8**; 2.0)
	Day (22/50)/Day 1	24.96 (22.3; 28.0)	13.09 (11.7; 14.7)	
A/H3N2	Baseline (Day 1)	72.96 (58.1; 91.6)	70.38 (55.9; 88.5)	
	Day 22/50	1153.4 (1035.4; 1284.9)	674.01 (604.4; 751.6)	1.71 (**1.6**; 1.8)
	Day (22/50)/Day 1	21.68 (19.5; 24.1)	12.67 (11.4; 14.1)	
B/Yamagata	Baseline (Day 1)	10.17 (9.0; 11.5)	10.12 (9.0; 11.4)	
	Day 22/50	198.89 (173.1; 228.5)	90.68 (78.8; 104.3)	2.19 (**2.0**; 2.4)
	Day (22/50)/Day 1	18.08 (15.7; 20.8)	8.25 (7.2; 9.5)	
B/Victoria[c]	Baseline (Day 1)	10.45 (9.6; 11.4)	10.36 (9.5; 11.3)	
	Day 22/50	315.52 (287.5; 346.3)	138.82 (125.2; 153.9)	2.27 (**2.0**; 2.6)
	Day (22/50)/Day 1	29.70 (26.9; 32.7)	13.28 (12.0; 14.7)	

Source: Table 14.1.1.1.5, Table 14.2.3.3.1.1 and Table 14.2.3.3.1.4
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; FAS=full analysis set; GMT=geometric mean titer; GMR=geometric mean ration; HI=hemagglutination inhibition; N=number of subjects with baseline and postbaseline serum samples; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine.
[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.
[b] A/H1N1=A/California/7/2009 pdm09-like virus, A/H3N2=A/Texas/50/2012, B/ Yamagata=B/Massachusetts/2/2012 and B/Victoria=B/Brisbane/60/2008.
[c] For B/Victoria results from Season 2 only are presented for both vaccine groups and used in the vaccine comparison analysis (N=745 for aQIV, N=738 for comparator).
Bold values indicate that superiority requirements were met.
Superiority criterion for the GMT ratio: The lower bound of the two-sided 95% CI on the adjusted ratio of GMTs for HI antibody titer should exceed 1.
Adjusted analysis GMT model: log-transformed postvaccination HI titer=log-transformed prevaccination HI titer+treatment group+ age group, health status+ season + country

Table 18: Number (%) of subjects with seroconversion (95%) and seroconversion differences (95% CI) at 21 Days after last vaccination against vaccine strains (superiority) in subjects ≥6 to <72 months of age – all seasons – FAS immunogenicity

Strain[b]	aQIV N=1481 n, % (95% CI)	Comparator[a] N=1405 n, % (95% CI)	Seroconversion Difference % (95% CI)
A/HINI	1115, 81.9 (79.7; 83.9)	963, 73.7 (71.2; 76.1)	8.2 (**5.0**; 11.3)
A/H3N2	1068, 78.4 (76.1; 80.6)	957, 73.2 (70.7; 75.6)	5.2 (**1.9**; 8.4)
B/Yamagata	1172, 86.0 (84.1; 87.8)	846, 64.7 (62.1; 67.3)	21.3 (**18.1**; 24.5)
B/Victoria[c]	678, 91.0 (88.8; 93.0)	571, 77.4 (74.2; 80.3)	13.6 (**10.0**; 17.3)

Source: Table 14.1.1.1.5, Table 14.2.3.6.1.1 and Table 14.2.3.6.1.4

Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; FAS=full analysis set; HI=hemagglutination inhibition; n=number of subjects with values in category; N =number of subjects with baseline and postbaseline serum samples; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine.

[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

[b] A/H1N1=A/California/7/2009 pdm09-like virus, A/H3N2=A/Texas/50/2012, B/ Yamagata=B/Massachusetts/2/2012 and B/Victoria=B/Brisbane/60/2008.

[c] For B/Victoria results from Season 2 only are presented for both vaccine groups and used in the vaccine comparison analysis (N=745 for aQIV, N=738 for comparator).

Bold values indicate that superiority requirements were met.

Superiority criterion for seroconversion: The lower bound of the two-sided 95% CI on the unadjusted difference of percentages of subjects seroconverted for HI antibody should exceed 0%.

Seroconversion is defined as HI ≥ 1:40 for subjects negative at baseline (ie, HI titer<1:10); or a minimum 4-fold increase in HI titer for subjects positive at baseline (ie, HI tier ≥ 1:10).

Antibody Titer Cut-off Analysis.

The reverse cumulative distributions of HI titers at 21 days after last vaccination have been provided for the A strains and B strains.

The HI titer categories at 21 days after last vaccination are reported for the homologous strain in the Table below, for the FAS.

Table 19: Number (%) of subjects with HI ≥1:110, ≥1:151, ≥1:215, ≥1: 330 and ≥1:629 (95% CI) at 21 Days after last vaccination in subjects ≥6 to <72 months of age – all seasons – FAS immunogenicity

Strain[b]		aQIV N=1481 n,% (95% CI)	Comparator[a] N=1405 n,% (95% CI)	Vaccine Group Difference (95% CI)
A/H1N1	HI ≥1:110	1325, 97.3 (96.3; 98.1)	1170, 89.5 (87.7; 91.1)	7.8 (5.9; 9.7)
	HI ≥1:151	1315, 96.5 (95.4; 97.5)	1134, 86.8 (84.8; 88.6)	9.8 (7.8; 11.9)
	HI ≥1:215	1280; 94.0 (92.6; 95.2)	1018, 77.9 (75.5; 80.1)	16.1 (13.5; 18.7)
	HI ≥1:330	1142, 83.8 (81.8; 85.8)	794, 60.7 (58.0; 63.4)	23.1 (19.8; 26.4)
	HI ≥1:629	1038, 76.2 (73.9; 78.5)	681, 52.1 (49.4; 54.8)	24.1 (20.6; 27.6)
A/H3N2	HI ≥1:110	1348, 99.0 (98.3; 99.4)	1216, 93.0 (91.5; 94.4)	5.9 (4.5; 7.5)
	HI ≥1:151	1340, 98.4 (97.6; 99.0)	1184, 90.6 (88.9; 92.1)	7.8 (6.1; 9.6)
	HI ≥1:215	1314, 96.5 (95.4; 97.4)	1108, 84.8 (82.7; 86.7)	11.7 (9.6; 13.9)
	HI ≥1:330	1218, 89.4 (87.7; 91.0)	920, 70.4 (67.8; 72.9)	19.0 (16.1; 22.0)
	HI ≥1:629	1147, 84.2 (82.2; 86.1)	825, 63.1 (60.4; 65.7)	21.1 (17.8; 24.3)
B/Yamagata	HI ≥1:110	945, 69.4 (66.9; 71.8)	531; 40.6 (38.0; 43.3)	28.8 (25.1; 32.3)
	HI ≥1:151	827, 60.7 (58.1; 63.3)	450, 34.4 (31.9; 37.1)	26.3 (22.6; 29.9)
	HI ≥1:215	621, 45.6 (42.9; 48.3)	311, 23.8 (21.5; 26.2)	21.8 (18.3; 25.3)
	HI ≥1:330	339, 24.9 (22.6; 27.3)	174, 13.3 (11.5; 15.3)	11.6 (8.6; 14.5)
	HI ≥1:629	221, 16.2 (14.3; 18.3)	123, 9.4 (7.9; 11.1)	6.8 (4.3; 9.4)
B/Victoria[c]	HI ≥1:110	1066, 78.3 (76.0; 80.4)	429, 58.1 (54.5; 61.7)	NA
	HI ≥1:151	1001, 73.5 (71.1; 75.8)	387, 52.4 (48.8; 56.1)	NA
	HI ≥1:215	849, 62.3 (59.7; 64.9)	285, 38.6 (35.1; 42.2)	NA
	HI ≥1:330	568, 41.7 (39.1; 44.4)	161, 21.8 (18.9; 25.0)	NA
	HI ≥1:629	434, 31.9 (29.4; 34.4)	125, 16.9 (14.3; 19.8)	NA

Source: Table 14.1.1.1.5 and Table 14.2.3.12.1

Abbreviations: aQIV = adjuvanted quadrivalent subunit influenza virus vaccine; CI = confidence interval; FAS=full analysis set; HI=hemagglutination inhibition; n=number of subjects with values in category; N =number of subjects with baseline and postbaseline serum samples; NA=not applicable; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine.

[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.

[b] A/H1N1=A/California/7/2009 pdm09-like virus, A/H3N2=A/Texas/50/2012, B/ Yamagata=B/Massachusetts/2/2012 and B/Victoria=B/Brisbane/60/2008.

[c] B/Victoria results from Season 1 and Season 2 (aQIV) and Season 2 (comparator) are presented. No comparison analysis for Season 2 data only was performed.

The percentage of subjects with HI titer of ≥1:110, ≥1:151, ≥1:215, ≥1:330 and ≥1:629 was higher in aQIV group than in the comparator vaccine group for all homologous strains in subjects ≥6 to <72 months of age at 21 days after the last vaccination.

The percentage difference (aQIV - comparator) in subjects achieving an HI titer of 1:629 against the homologous A/H1N1 and A/H3N2 strains were 24.1% and 21.1%, respectively, for V118_05. The same trends in differences in percentages of subjects reaching the specified threshold titers were observed for the B vaccine strains

In both Study V118_05 these differences in proportion of subjects reaching threshold titers between aQIV and comparator started around HI titers of ≥1:215 in the A strains, but at lower HI titers of ≥1:40 or ≥1:110 in the B strain(s).

Immune Response by Vaccine Naivety Status

Overall, in all comparisons the aQIV group had higher GMT values, SCRs, and percentages of subjects with HI titer ≥1:40 than the comparator group after the first (non-naïve) and second vaccinations (naïve). After the first vaccination the GMT titers for vaccine naïve subjects were lower than those obtained in non-naïve vaccine subjects.

Dose Group

In Study V118_05, subjects received a dose of 0.25 mL if they were aged 6 to <36 months at study Day 1, or 0.50 mL if they were aged 36 to <72 months at study Day 1.

As indicated in Table 21 aQIV elicited a superior immunogenic response based on the lower limit of the 95% CI of the GMT ratio [GMTaQIV/GMTcomparator]) above 1 for all homologous strains tested relative to the comparator vaccine for the pre-specified groups of 0.25 mL dose and 0.5 mL dose. Higher GMT ratios were observed in subjects from the 0.25 mL dose group.

Table 20: study V118_5 – Immunogenicity results (GMT, GMR and GMT ratio) against vaccine strains (superiority) at 21 days after last vaccination in subjects by dose group (0.25ml or 0.5ml) – All seasons – FAS Immunogenicity

Dose Group (Age Group)		0.25 mL (6 to <36 Months)			0.5 mL (36 to <72 Months)		
		aQIV	Comparator[a]	GMT Ratio (95% CI)	aQIV	Comparator[a]	GMT Ratio (95% CI)
		N=822	N=798		N=659	N=607	
Strain[b]		GMT/GMR (95% CI)	GMT/GMR (95% CI)		GMT/GMR (95% CI)	GMT/GMR (95% CI)	
A/H1N1	Baseline (Day 1)	17.18 (15.2; 19.4)	17.59 (15.6; 19.9)		114.32 (98.6; 132.5)	106.47 (91.0; 124.6)	
	Day 22/50	740.40 (689.3; 795.3)	316.28 (286.2; 349.5)	2.34 (**2.1**; 2.6)	1306.90 (1227.5; 1391.5)	879.76 (811.6; 953.6)	1.49 (**1.3**; 1.6)
	Day (22/50)/Day 1	42.69 (37.9; 48.1)	18.13 (16.1; 20.4)		11.46 (10.1; 13.1)	8.22 (7.2; 9.4)	
A/H3N2	Baseline (Day 1)	26.13 (22.7; 30.0)	24.25 (21.2; 27.7)		135.17 (116.8; 156.4)	133.16 (113.8; 155.8)	
	Day 22/50	1035.62 (969.0; 1106.8)	486.78 (446.1; 531.2)	2.13 (**1.9**; 2.4)	1372.18 (1292.3; 1457.0)	1030.19 (951.2; 1115.8)	1.33 (**1.2**; 1.5)
	Day (22/50)/Day 1	39.45 (34.3; 45.4)	20.41 (18.1; 23.1)		10.20 (8.9; 11.7)	7.71 (6.8; 8.8)	
B/Yamagata	Baseline (Day 1)	8.44 (7.9; 9.0)	8.89 (8.3; 9.5)		15.19 (13.9; 16.6)	14.01 (12.7; 15.4)	
	Day 22/50	145.66 (133.9; 158.4)	52.20 (47.4; 57.5)	2.79 (**2.5**; 3.2)	225.05 (205.7; 246.2)	137.42 (123.9; 152.4)	1.64 (**1.4**; 1.9)
	Day (22/50)/Day 1	17.35 (15.8; 19.1)	5.91 (5.4; 6.5)		14.52 (13.2; 16.0)	9.70 (8.7; 10.8)	
B/Victoria[c]	Baseline (Day 1)	6.38 (5.9; 6.8)	6.87 (6.3; 7.5)		16.51 (14.4; 18.9)	15.18 (13.2; 17.4)	
	Day 22/50	250.93 (217.7; 289.2)	89.78 (77.2; 104.5)	2.79 (**2.3**; 3.4)	384.84 (341.4; 433.8)	205.25 (180.3; 233.7)	1.87 (**1.6**; 2.2)
	Day (22/50)/Day 1	39.69 (34.4; 45.8)	13.00 (11.3; 15.0)		23.09 (20.3; 26.3)	13.53 (11.8; 15.5)	

Source: CSR V118_05, Table 14.1.1.1.6, Table 14.2.3.3.1.2 and Table 14.2.3.3.1.10.

Abbreviations: aQIV=adjuvanted quadrivalent influenza vaccine; CI=confidence interval; FAS=full analysis set; GMT=geometric mean titer; HI=hemagglutination inhibition; N=number of subjects with baseline and postbaseline serum samples, for individual time points by strain refer to the source table in the CSRs; QIV-1 = quadrivalent influenza vaccine 1; TIV-1 = trivalent influenza vaccine 1.

[a] Comparator vaccine included TIV-1 (Season 1) and QIV-1 (Season 2).

[b] For the specific virus strains tested, see Table 1-5.

[c] For B/Victoria, results from Season 2 only are presented for both vaccine groups and used in the vaccine comparison analysis for both age groups.

Notes: **Bold** values indicate that superiority requirements were met.

Superiority criterion for the GMT ratio: The lower bound of the two-sided 95% CI on the adjusted ratio of GMTs for HI antibody titer should exceed 1.

Heterologous Immune Response

Heterologous A/H1N1 immune responses postvaccination were close to baseline for both vaccines.

The GMTs at 21 days after last vaccination are reported for heterologous strains in

Table 22, for the FAS.

The baseline GMTs for all heterologous strains were comparable for aQIV and comparator vaccine groups in subjects ≥6 to <72 months of age. The GMTs for heterologous A/H3N2 and the B heterologous strains were higher in aQIV group than in the comparator vaccine group at 21 days after the last vaccination. The LL of the 2-sided 95% CI of the GMTr was >1.5 for heterologous A/H3N2 and the B heterologous strains.

Table 21: Geometric Mean HI titers, GMR, GMT ratios and GMT ratios (95%) against heterologous strains at 21 Days after last vaccination in subjects ≥6 to <72 months of age – All seasons – FAS Heterologous Immunogenicity

Heterologous Strain[b]		aQIV N=297 GMT/GMR (95% CI)	Comparator[a] N=295 GMT/GMR (95% CI)	GMT Ratio (95% CI)
A/H1N1	Baseline (Day 1)	5.78 (4.9; 6.8)	5.56 (4.7; 6.5)	
	Day 22/50	7.46 (6.3; 8.9)	6.52 (5.5; 7.8)	1.14 (1.1; 1.2)
	Day (22/50)/Day 1	1.33 (1.1; 1.6)	1.16 (1.0; 1.4)	
A/H3N2	Baseline (Day 1)	51.62 (28.4; 93.7)	53.05 (28.9; 97.3)	
	Day 22/50	576.84 (407.4; 816.7)	297.70 (209.0; 424.1)	1.94 (1.6; 2.3)
	Day (22/50)/Day 1	22.30 (15.7; 31.6)	11.51 (8.1; 16.4)	
B/Yamagata	Baseline (Day 1)	7.97 (5.9; 10.8)	8.35 (6.1; 11.4)	
	Day 22/50	145.89 (98.3; 216.6)	67.24 (45.0; 100.5)	2.17 (1.8; 2.6)
	Day (22/50)/Day 1	16.80 (11.3; 24.9)	7.74 (5.2; 11.6)	
B/Victoria[c]	Baseline (Day 1)	9.49 (8.1; 11.1)	9.18 (7.9; 10.7)	
	Day 22/50	186.65 (157.3; 221.5)	88.09 (73.0; 106.3)	2.12 (1.6; 2.7)
	Day (22/50)/Day 1	19.83 (16.2; 24.3)	9.55 (7.9; 11.6)	

Source: Table 14.1.1.1.5, Table 14.2.3.3.3.1 and Table 14.2.3.3.3.4
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; GMT=geometric mean titer; GMR=geometric mean ratio; FAS=full analysis set; HI=hemagglutination inhibition; N=number of subjects with baseline and postbaseline serum samples; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine.
[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.
[b] H1N1=A/Brisbane/59/2007- like; H3N2 =A/Hong Kong/4801/2014; B/Yamagata=B/Phuket/3073/2013-like; B Victoria=B/Malaysia/2506/2004.
[c] For B/Victoria results from Season 2 only are presented for both vaccine groups and used in the vaccine comparison analysis (N= 141 for aQIV, N= 158 for comparator).
Adjusted analysis GMT model: log-transformed postvaccination HI titer=log-transformed prevaccination HI titer+treatment group+ age group, health status+ season + country.

Correlate of Protection

A correlate of protection (CoP) analysis was performed to estimate the relationship between post vaccination HI titers and protection from influenza disease.

The numbers of reported influenza cases due to A/H1N1, B/Yamagata, and B/Victoria strains in the immunogenicity subset were low and insufficient for the analysis. The CoP analysis was therefore limited to the A/H3N2 strain. The majority of A/H3N2 influenza cases were reported during Season 2 and were assessed to be mismatched to the vaccine strain.

An observed CoP HI titer for homologous A/H3N2 of 1,041.1 (95% CI: 705.42; 1,536.46) was associated with 50% protection against RT-PCR confirmed A/H3N2 infection, i.e., including the infections resulting from the A/H3N2 drifted strains. This observed CoP was significantly higher than previously reported in the literature for studies performed in A/H3N2 matched seasons, which suggest that the protection threshold may vary from year to year and may depend on the level of similarity between the vaccine strain and circulating strains.

Immune Responses Measured by Microneutralization

From the Immunogenicity subset, an additional subset (600 subjects) was randomly selected after enrollment was completed.

The antibody response (GMT, geometric mean ratio [GMR], and GMTr) against the most prevalent influenza strains (A/H3N2 and B/Yamagata) during the study period was assessed by an MN assay as an exploratory analysis.

The GMTs and GMRs at 21 days and 180 days after last vaccination in subjects ≥6 to <72 months of age are reported in the Table below for the FAS MN Immunogenicity.

Table 22: Geometric Mean MN Titers, Geometric Mean Ratios, GMT Ratios and GMT Ratios (95% CI) Against A/H3N2 and B/Yamagata Vaccine strains at Day 22/50 and Day 181/209 in subjects ⩾6 to <72 months of age – FAS MN Immunogenicity

Table 9: Geometric Mean MN Titers, Geometric Mean Ratios, GMT Ratios and GMT Ratios (95% CI) Against A/H3N2 and B/Yamagata Vaccine Strains at Day 22/50 and Day 181/209 in Subjects ≥6 to <72 Months of Age – FAS MN Immunogenicity

Strain[b]	aQIV N = 300 GMT/GMR (95% CI)	Comparator[a] N = 297 GMT/GMR (95% CI)	GMT Ratio (95% CI)
A/H3N2			
Day 1	93.57 (48.4; 180.9)	96.82 (49.5; 189.5)	
Day 22/50	2809.52 (1826.0; 4322.8)	1396.47 (900.5; 2165.6)	**2.01 (1.6; 2.5)**
Day (22/50)/Day 1	43.66 (28.4; 67.2)	21.70 (14.0; 33.7)	
Day 181/209	852.72 (552.2; 1316.8)	493.51 (317.0; 768.3)	**1.73 (1.4; 2.1)**
Day (181/209)/Day 1	12.97 (8.4; 20.0)	7.51 (4.8; 11.7)	
B/Yamagata			
Day 1	7.58 (5.2; 11.0)	8.54 (5.9; 12.4)	
Day 22/50	323.21 (207.6; 503.1)	136.69 (87.2; 214.3)	**2.36 (1.9; 2.9)**
Day (22/50)/Day 1	32.29 (20.7; 50.3)	13.66 (8.7; 21.4)	
Day 181/209	60.54 (41.4; 88.5)	33.26 (22.6; 48.9)	**1.82 (1.5; 2.2)**
Day (181/209)/Day 1	6.06 (4.1; 8.9)	3.33 (2.3; 4.9)	

Source: Table 14.1.2.1 and Table 14.2.3.30.3.
Abbreviations: ANCOVA=analysis of covariance; aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; CI=confidence interval; FAS=full analysis set; GMT=geometric mean titer; GMR=geometric mean ratio; MN=microneutralization; N=number of subjects with reportable results for baseline and post-baseline samples. The actual number of results may vary by time point and strain; QIV=quadrivalent influenza vaccine; TIV=trivalent subunit influenza virus vaccine.
Statistical model used: PROC GLM logtiter=arm logbase age group 'health status' season country. Note that age group is from planned randomization.
Adjusted GMT, GMR, and 95% CI are analyzed using analysis of covariance (ANCOVA) with covariates as specified in the statistical model above.
[a] Nonadjuvanted TIV administered in Season 1 and nonadjuvanted QIV administered in Season 2.
[b] A/H3N2=A/Texas/50/2012 and B/Yamagata=B/Massachusetts/2/2012.

As can be seen in the Table GMTs were consistently higher at Day 22/50 in the aQIV group than in the comparator for both strains tested and enhanced persistence of immune response with aQIV was observed in that Day 181/209 GMTs were consistently higher in aQIV for both strains tested. At Day 22/50, the GMTr was >2-fold with a lower limit (LL) of the 95% CI above 1.5 for both strains.

Other analyses performed comparing seroprotection and seroconversion rates, as well as subgroup analyses age group and vaccination status, generally showed that aQIV was more immunogenic than the comparator vaccine

Ancillary analyses

Persistence of Immune Response against Homologous Strains

The greater immunogenicity of aQIV relative to the comparator vaccine in subjects 6 to <72 months of age was evident at 180 days after the last vaccination in Study V118_05. Persistent immune response

6 months after vaccination was also observed in the two revaccinations studies (see data below), and supported by the findings in the aTIV studies (CSR V70_29 and CSR V70P2). Persistence of the greater antibody response up to 12 months after vaccination was evident from the baseline titers obtained in both revaccination studies one season following priming in V118_05.

In V118_05E1 (revaccination after Season 1 of V118_05), the vaccine strains were identical to those received during priming in Study V118_05. Results show the greater baseline titers for aQIV (versus QIV-1) in the revaccination study V118_05E1 for both A strains and B/Yamagata. Comparisons of B/Victoria are not presented as this strain was not included during priming with the comparator vaccine (TIV-1) during Season 1 in V118_05.

In V118_05E3 (revaccination after Season 2 of V118_05), baseline titers were combined for the treatment groups (aQIV/aQIV and aQIV/QIV-1 as well as for QIV-1/aQIV and QIV 1/QIV 1) and presented for the A/H1N1 and B/Victoria strains that were the same as used during priming in V118_05 one year earlier.

In all cases, the lower limit of the 95% CI of the GMT ratio of aQIV versus comparator for the HI titers at least 6 months following vaccination is equal or above 1.3 (Table 24).

Table 23: antibody persistence (geometric mean titers and geometric mean tier ratios) for homologous strains at 6 and up to 12 months after vaccination

	GMT		GMT Ratio (95% CI)
Day 181/209 / Day 365[a] / Day 365[c]	aQIV N=1284 / N=309 / N=806	Comparator[a] N=1239 / N=273 / N=795	aQIV: Comparator
A/H1N1			
Day 181/209	351.59	189.43	1.86 (1.7; 2.0)
Day 365 (V118_05E1)[b]	242.81	116.87	2.08 (1.7; 2.6)
Day 365 (V118_05E3)[c]	215.14	113.26	1.90 (1.6; 2.2)
A/H3N2			
Day 181/209	458.07	290.88	1.57 (1.4; 1.7)
Day 365 (V118_05E1)[b]	325.38	140.62	2.31 (1.8; 3.0)
B/Yamagata			
Day 181/209	48.65	26.22	1.86 (1.7; 2.0)
Day 365 (V118_05E1)[b]	27.97	14.77	1.89 (1.6; 2.3)
B/Victoria			
Day 181/209[d]	65.78	36.46	1.80 (1.6; 2.1)
Day 365 (V118_05E1)[b]	45.60	NA	NA
Day 365 (V118_05E3)[c]	59.08	39.78	1.49 (1.3; 1.7)

Source: CSR V118_05, CSR V118_05E1, CSR V118_05E3 (additional post-hoc analysis was performed).
Abbreviations: aQIV=adjuvanted quadrivalent influenza vaccine; CI = confidence interval; GMT = geometric mean titer; N=number of subjects with baseline and postbaseline serum samples at the applicable time point, for individual strains refer to the source table in the CSRs; NA = not applicable; QIV-1=quadrivalent influenza vaccine 1; TIV-1=trivalent influenza vaccine 1.

[a] In Study V118_05, comparator vaccine included TIV-1 (Season 1) and QIV-1 (Season 2). In Studies V118_05E1 and V118_05E3, comparator vaccine was QIV-1.

[b] Baseline values (unadjusted) from V118_05E1. Results from B/Victoria are not presented (NA) for the comparator vaccine as this vaccine did not include the B/Victoria strain during priming in V118_05. Note that subjects in V118_05 could be revaccinated in V118_05E1 at 6 months after last vaccination. Approximately 85% of subjects with baseline titers in V118_05E1 had this sample collected at 9 to 12 months following last vaccination in V118_05.

[c] Baseline values (unadjusted) from V118_05E3 for the strains that were used during the priming in V118_05, ie, A/H1N1 and B/Victoria. Different strains were recommended for inclusion in the influenza vaccines for A/H3N2 and B/Yamagata during Season 2015/2016. Note that the baseline results were obtained from mainly different subjects than included in the immunogenicity subset in V118_05 with subjects in V118_05E3 mainly enrolled from Asia.

[d] For Study V118_05, B/Victoria results from Season 2 only are presented as this strain was not included in the comparator vaccine (TIV-1).

Note: For the specific virus strains tested in each study, see Table 1-5.

Immune Response upon Revaccination

Study V118_05 was conducted over two seasons. After Season 1, subjects from a selected group of sites were invited to enroll in revaccination study V118_05E1. Similarly, after Season 2, subjects from a selected group of sites were invited to enroll in revaccination study V118_05E3.

Study V118_05E1 was a revaccination study, wherein subjects were vaccinated approximately 9 to 12 months after the initial vaccinations in the parent study V118_05 and the randomization was carried over from V118_05: subjects received the same influenza vaccine and the same strains as administered in the pivotal study, i.e., aQIV or licensed non-adjuvanted comparator influenza vaccine. However, subjects assigned to the licensed comparator group received the trivalent influenza vaccine (TIV 1) in clinical study V118_05 and were therefore not previously exposed to B/Victoria (B/Brisbane/60/2008) strain.

Study V118_05E3 was a revaccination study in which subjects were re-randomized to receive the same or different quadrivalent vaccine type (adjuvanted or nonadjuvanted) from what they had received in Study V118_05, which resulted in 4 treatment groups (aQIV/aQIV; aQIV/QIV-1; QIV-1/aQIV; QIV-1/QIV-1). Vaccine strains for A/H1N1 and for B/Victoria where the same as those included in the V118_05 study, while the A/H3N2 and B/Yamagata strains were updated in accordance with the latest WHO recommendations.

Study populations in the revaccination studies were, as expected due to the sequential nature, slightly older compared to the parent study, but otherwise largely similar for gender distribution and health status. Differences in race originated from difference in countries that were enrolling subjects.

HI data

An overview of the GMTs against the homologous strains at baseline and on Day 22 and Day 181 and vaccine group comparisons by means of GMT ratios on Day 22 and Day 181 were provided in the application. The main results are summarized here:

- Baseline GMTs were higher across all strains in subjects who received aQIV in the parent study when compared to subjects who received QIV-1 or TIV-1 in the parent study, reflecting higher persistence of immune response in the aQIV group.
- For subjects who were primed with aQIV in Study V118_05, significantly higher immune response was observed for 3 out of 4 strains (A/H1N1 and both B strains) upon revaccination with aQIV compared to QIV-1 (V118_05E3).
- The immune responses of the treatment groups with different vaccines used for priming and revaccination (i.e., aQIV/QIV-1 and QIV-1/aQIV) were intermediate between the repeated adjuvanted and repeated non-adjuvanted groups, in general (V118_05E3).
- After repeat vaccination with aQIV in V118_05E1 and V118_05E3, a significantly higher immune response was observed when compared to subjects that received repeat non-adjuvanted vaccine for all strains, except for A/H3N2 on Day 22 in study V118_05E3.

Table 24: Study V118_05E1 and study V118_05E3 – Geometric Mean Titer (95% CI) at Baseline and 21 and 180 days after vaccination in subjects 12 months to < 7 years of age – FAS immunogenicity

		V118_05E1		V118_05E3			
Vaccine in Study V118_05		aQIV	TIV-1	aQIV	aQIV	QIV-1	QIV-1
Vaccine in revaccination study		aQIV	QIV-1	aQIV	QIV-1	aQIV	QIV-1
		N=309	N=273	N=403	N=403	N=401	N=394
A/H1N1	Day 1	320.27 (261.9; 391.6)	165.23 (134.0; 203.8)	165.00 (139.2, 195.6)	151.63 (128.3, 179.2)	81.51 (68.8, 96.6)	84.42 (71.2, 100.1)
	Day 22	1036.27 (923.2; 1163.2)	700.78 (623.7; 787.3)	1218.91 (1137.0, 1306.7)	1023.37 (955.7, 1095.8)	1205.80 (1123.8, 1293.8)	875.19 (815.7, 939.1)
	Day 181	424.00 (374.2; 480.5)	282.31 (248.8; 320.4)	489.02 (449.4, 532.1)	413.15 (380.2 , 448.9)	425.48 (390.6, 463.5)	308.68 (283.3, 336.3)
A/H3N2	Day 1	336.88 (268.5; 422.7)	155.97 (123.1; 197.6)	154.09 (129.9, 182.7)	159.93 (135.3, 189.1)	100.69 (84.9, 119.4)	99.73 (84.1, 118.3)
	Day 22	1221.47 (1093.1; 1364.9)	908.63 (810.0; 1019.3)	2345.71 (2216.8, 2482.1)	2521.60 (2385.4, 2665.6)	2361.41 (2229.1, 2501.6)	2231.18 (2105.8, 2364.0)
	Day 181	611.09 (529.0; 705.9)	454.46 (391.5; 527.6)	1408.49 (1296.0, 1530.8)	1423.45 (1311.7, 1544.7)	1221.54 (1122.0, 1329.9)	1212.04 (1113.0, 1319.9)
B/Yamagata	Day 1	32.36 (26.9; 38.9)	17.78 (14.7; 21.5)	35.57 (31.9, 39.6)	35.54 (32.0, 39.5)	21.00 (18.8, 23.4)	22.23 (19.9, 24.8)
	Day 22	176.04 (150.8; 205.5)	100.80 (86.1; 118.1)	274.75 (251.1, 300.6)	230.51 (211.0, 251.9)	219.20 (199.9, 240.3)	154.97 (141.4, 169.9)
	Day 181	54.08 (46.6; 62.8)	29.26 (25.1; 34.1)	95.56 (87.2, 104.7)	85.25 (77.9, 93.3)	71.00 (64.6, 78.0)	55.99 (51.0, 61.5)
B/Victoria	Day 1	46.41 (38.0; 56.6)	14.33 (11.6; 17.6)	47.91 (41.3, 55.5)	42.98 (37.2, 49.7)	30.23 (26.1, 35.0)	30.63 (26.4, 35.5)
	Day 22	244.52 (203.6; 293.7)	163.95 (135.6; 198.2)	387.35 (354.1, 423.7)	326.68 (299.1, 356.8)	327.97 (299.6, 359.0)	246.06 (224.8, 269.4)
	Day 181	65.85 (55.9; 77.6)	50.88 (42.9; 60.3)	126.45 (113.4, 141.0)	113.95 (102.3, 126.9)	102.14 (91.5, 114.0)	78.53 (70.3, 87.7)

	V118_05E1		V118_05E3			
Vaccine in Study V118_05	aQIV	TIV-1	aQIV	aQIV	QIV-1	QIV-1
Vaccine in revaccination study	aQIV	QIV-1	aQIV	QIV-1	aQIV	QIV-1
	N=309	N=273	N=403	N=403	N=401	N=394

Source: V118_05E1 CSR, Table 14.2.1.1.1.1; V118_05E3 CSR Table 14.2.1.1.1.

Abbreviations: aQIV=adjuvanted quadrivalent influenza vaccine; CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer; N=number of subjects with baseline and postbaseline serum samples, for individual time points by strain refer to the source table in the CSRs; QIV-1=quadrivalent influenza vaccine 1; TIV-1=trivalent influenza vaccine 1.

Note: Subjects assigned to the comparator group in V118_05E1 received trivalent influenza vaccine 1 (TIV-1) in clinical study V118_05 and were not exposed to B/Victoria (B/Brisbane/60/2008) strain before; refer to Table 1.5 for all strain details.

Table 25: Study V118_05E1 and study V118_05E3 – Geometric Mean Titer Ratio (95% CI) at Baseline and 21 and 181 days after vaccination in subjects 12 months to < 7 years of age – FAS immunogenicity

		Revaccination with the same vaccine		Revaccination after priming with QIV	Revaccination after priming with aQIV
		V118_05E1	V118_05E3	V118_05E3	V118_05E3
		aQIV/aQIV vs TIV/QIV	aQIV/aQIV vs QIV/QIV	QIV/aQIV vs QIV/QIV	aQIV/aQIV vs aQIV/QIV
A/H1N1	Day 22	1.48 (1.3; 1.7)	1.39 (1.28, 1.52)	1.38 (1.27, 1.50)	1.19 (1.10, 1.30)
	Day 181	1.50 (1.3; 1.7)	1.58 (1.43, 1.76)	1.38 (1.25, 1.53)	1.18 (1.07, 1.31)
A/H3N2	Day 22	1.34 (1.2; 1.5)	1.05 (0.98, 1.13)	1.06 (0.99, 1.13)	0.93 (0.87, 1.0)
	Day 181	1.34 (1.2; 1.6)	1.16 (1.05, 1.28)	1.01 (1.91, 1.13)	0.99 (0.90, 1.09)
B/Yamagata	Day 22	1.75 (1.5; 2.0)	1.77 (1.59, 1.98)	1.41 (1.27, 1.58)	1.19 (1.07, 1.33)
	Day 181	1.85 (1.6; 2.2)	1.71 (1.53, 1.91)	1.27 (1.14, 1.42)	1.12 (1.00, 1.25)
B/Victoria	Day 22	1.49 (1.2; 1.8)	1.57 (1.41, 1.76)	1.33 (1.20, 1.49)	1.19 (1.07, 1.32)
	Day 181	1.29 (1.1; 1.5)	1.61 (1.41, 1.84)	1.30 (1.14, 1.48)	1.11 (0.97, 1.27)

Source: CSR V118_05E3 Table 14.2.3.1.1 and Table 14.2.1.1.1; CSR V118_05E1 Table 14.2.1.1.1.1

Abbreviations: aQIV=adjuvanted quadrivalent influenza vaccine; CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer; QIV-1=quadrivalent influenza vaccine 1; TIV-1=trivalent influenza vaccine 1.

Note: For the specific virus strains tested in each study, see Table 1-5.

Microneutralization Data

MN GMT, GMR, and GMT Ratio Assessed by Microneutralization. The antibody response (MN GMT, GMR, and GMTr) against the homologous strains contained in the study vaccine was additionally assessed by MN assay, to further characterize the immune response in a subset of approximately 240 subjects.

Adjusted MN GMTs and GMRs on Day 22 and Day 181 were presented for the 4 homologous strains for the PPS.

In general, MN GMTs were highest in aQIV/aQIV, results for aQIV/QIV and QIV/aQIV were similar and slightly lower, and MN GMTs were lowest for the QIV/QIV group.

Antibody response against homologous strains by anti-NA assay

The antibody response (anti-NA GMT, GMR, and GMTr) against the homologous strains contained in the study vaccine was additionally assessed by anti-NA assay, to further characterize the immune response in a subset of 240 subjects.

- For all strains tested, baseline (Day 1) anti-NA GMTs were generally higher in the aQIV primed group compared to the QIV-1 primed group in the parent study.
- Both on Day 22 and on Day 181, anti-NA GMTs were similar in the aQIV/aQIV, aQIV/QIV-1, and QIV-1/aQIV groups and were notably higher compared with the repeated nonadjuvanted group in all strains except for N2 antibodies, which showed no notable difference between treatment groups

2.5.2.1.1. 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 26: Summary of efficacy for trial V118_05

Title: A Phase III, Stratified, Randomized, Observer Blind, Controlled, Multicenter Clinical Study to Evaluate the Safety, Immunogenicity and Efficacy of an Adjuvanted Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-adjuvanted Comparator Influenza Vaccine in Children ≥6 to <72 Months of Age.		
Study identifier	V118_05	
Design	Phase 3, observer blind, stratified, randomized, group-sequential, multicentre	
	Duration of main phase:	The subjects in this study were enrolled over at least 2 influenza seasons. Date of first enrollment: 03 November 2013 Date of last completed: 25 April 2016
Hypothesis	Superiority (clinical efficacy)	
Treatments groups	aQIV	MF59 adjuvanted quadrivalent influenza vaccine; 5352 subjects
	QIV/TIV	Non-adjuvanted tri- (season 1) or quadrivalent (season 2) influenza vaccine; 5292 subjects

Endpoints and definitions	Primary endpoint	rVE	Estimate of relative Vaccine Efficacy of aQIV to QIV/TIV for preventing first-occurrence RT-PCR-confirmed influenza disease caused by influenza strains related to those contained in aQIV and non-adjuvanted comparator in children ⩾6 to <72 months of age, for ILI cases occurring at ⩾21 days and ⩽ 180 days after the last vaccination or until the end of the influenza season.
	Secondary endpoints	Efficacy endpoints. Only the most relevant ones are shown: The following objective was evaluated on first-occurrence RT-PCR-confirmed influenza in all subjects in the following age groups: ≥6 to <24 months of age, ≥6 to <36 months of age and ≥36 to <72 months of age. • To evaluate the relative efficacy of aQIV compared to non-adjuvanted comparator as determined by the proportion of subjects with first-occurrence RT-PCR-confirmed influenza A and/or B of any influenza strain. The following objectives were evaluated on first-occurrence culture-confirmed influenza in all subjects in the following age groups: ≥6 to <72 months of age, ≥6 to <24 months of age, ≥6 to <36 months of age and ≥36 to <72 months of age. • To evaluate the relative efficacy of aQIV compared to non-adjuvanted comparator as determined by the proportion of subjects with first-occurrence influenza caused by culture-confirmed strains A and/or B regardless of antigenic match to those contained in the vaccines. • To evaluate the relative efficacy of aQIV compared to non-adjuvanted comparator as determined by the proportion of subjects with first-occurrence RT-PCR-confirmed influenza A and/or B of any influenza strain in subjects ≥6 to <72 months of age at ≥7 days and at ≥14 days after the first vaccination up to the day of the second vaccination in vaccine naïve subjects only.	
	Secondary endpoints	Immunogenicity endpoints. Only the most relevant ones are shown: • To demonstrate noninferiority of HI antibody responses to aQIV vs. TIV/QIV against each of the 3 strains contained in TIV (A/H1N1, A/H3N2 and B/Yamagata) and against each of the 4 strains as contained in QIV (A/H1N1, A/H3N2, B/Yamagata and B Victoria) in terms of ratio of geometric mean titer (GMT) and differences in the proportion of subjects with seroconversion (SC) 21 days after the last vaccination in subjects ⩾6 to <72 months of age. • To demonstrate superiority of HI antibody responses to aQIV vs TIV/QIV against each of the 3 strains contained in TIV (A/H1N1, A/H3N2 and B/Yamagata) and against each of the 4 strains as contained in QIV (A/H1N1, A/H3N2, B/Yamagata and B Victoria) in terms of ratio of GMT and differences in the proportion of subjects with SC 21 days after the last vaccination in subjects ⩾6 to <72 months of age.	
Database lock	28 September 2016.		

Results and Analysis

Analysis description	**Primary Analysis**

Analysis population and time point description	FAS Efficacy Cases occurring 21 days and ⩽ 180 days after the last vaccination or until the end of the influenza season.		
Descriptive statistics and estimate variability [Efficacy Analyses]	**Treatment group**	**aQIV**	**QIV/TIV**
	Number of subject	5278	5193
	RT-PCR confirmed ILI cases overall	256 (4.9%)	252 (4.9%)
	RT-PCR confirmed ILI cases A/H1N1	7 (0.1%)	17 (0.3%)
	RT-PCR confirmed ILI cases A/H3N2	200 (3.8%)	196 (3.8%)
	RT-PCR confirmed ILI cases B/Yamagata	36 (0.7%)	36 (0.7%)
	RT-PCR confirmed ILI cases B/Victoria	14 (0.3%)	9 (0.2%)
Analysis description	**Immunogenicity analysis**		
Analysis population and time point description	FAS Immunogenicity Titres determined 21 days after last vaccination.		
Descriptive statistics and estimate variability [Immunogenicity Analyses]	**Treatment group**	**aQIV**	**QIV/TIV**
	Number of subjects	1481	1405
	GMT D22/50 A/H1N1 (95%CI)	996.40 (888.4 , 1117.6)	522.50 (465.3 , 586.7)
	GMT D22/50 A/H3N2 (95%CI)	1153.40 (1035.4 , 1284.9)	674.01 (604.4 , 751.6)
	GMT D22/50 B/Yam (95%CI)	198.89 (173.1 , 228.5)	90.68 (78.8 , 104.3)
	GMT D22/50 B/Vic (95%CI)	297.81 (256.1 , 346.3)	131.09 (110.0 , 156.2)

Effect estimate per comparison	**Primary endpoint (rVE)**	**Comparison groups**			**aQIV to QIV/TIV**	
		rVE (%)			-0.67	
		95% CI			-19.81 - 15.41	
		P-value			*ND*	
	Secondary endpoint (rVE per strain)	aQIV to QIV/TIV				
			A/H1N1	A/H3N2	B/Yam	B/Vic
		rVE (%)	59.4	-1.3	2.1	-54.5

		95% CI	2.1 – 83.2	-23.4 – 16.8	-55.4 – 38.3	-256.9 – 33.1
		P-value	*ND*	*ND*	*ND*	*ND*
	Secondary endpoint (GMTr)		A/H1N1	A/H3N2	B/Yam	B/Vic
		GMTr	1.91	1.71	2.19	N/A
		95% CI	1.8 – 2.0	1.6 – 1.8	2.0 – 2.4	
		P-value	*ND*	*ND*	` *ND*	*ND*
Secondary endpoint results	•Efficacy results: only the most relevant results are shown: •There was no difference in relative efficacy between aQIV and comparator vaccine for any culture-confirmed or matched or unmatched influenza strains in subjects ≥6 to <72 months of age. • Greater vaccine efficacy was demonstrated in children ≥6 to <24 months; the rVE estimate for any strain detected by RT-PCR was 31.37 (95% CI: 3.14; 51.38). •There was a benefit of aQIV relative to the comparator vaccine in preventing early cases of influenza shortly after vaccination. rVE was 54.66 (95% CI: 18.08; 74.91) and 70.56 (35.19; 86.62) ≥7 and ≥14 days after first and up to second vaccination, respectively in vaccine naïve subjects indicating higher early efficacy of aQIV than the comparator vaccine.					
Secondary endpoint results	Immunogenicity results: only the most relevant results are shown: • aQIV elicited a superior immunogenic response (as reflected by GMT ratio [GMTaQIV/GMTcomparator]), having a lower 95% CI limit >1 and SC difference with a lower 95% CI limit >0 for all homologous strains tested relative to the comparator vaccine for all prespecified age groups. The LL of the 2-sided 95% CI of the GMTr exceeded 1.5 for all homologous strains. The highest GMT ratios were observed in subjects aged ≥6 to < 24 months ranging from 2.58 (95% CI: 2.2; 3.0) for A/H3N2 to 3.84 (95% CI: 2.9; 5.0) for B/Victoria.					

2.5.3. Supportive studies (paediatric indication)

Supportive Studies with aTIV

This section summarizes immunogenicity results individually from the 5 supportive studies that compare the immunogenicity of aTIV versus TIV. An overview of these studies has been shown in the table overview of clinical studies.

Evaluation of Immune Response against Homologous Strains

The summary provided here for each study is based on the primary analysis population pre-specified in the protocol and its accompanying SAP; this was typically the PPS unless specified otherwise.

Overall, there was a consistent trend of greater immunogenicity in adjuvanted vaccine groups compared to non-adjuvanted vaccine groups across all 6 aQIV/aTIV clinical studies in terms of GMTs at Day 22/Day 50 (approximately 3 weeks after last vaccination), GMRs, and SCRs against homologous strains (Table 30). In pivotal study V118_05, the aQIV group's GMTs, GMRs, and SCRs were higher than for the comparator group for all 4 strains. Similarly, the 5 aTIV studies consistently elicited a greater postvaccination immune response in terms of GMTs, GMRs, and SCRs than non-adjuvanted groups. The greater immune response is confirmed by the higher GMT ratios at Day 22/Day 50 (approximately 3 weeks after last vaccination) against homologous strains in adjuvanted vaccine groups compared to non-adjuvanted vaccine groups across all 6 aQIV/aTIV studies, as indicated in Table 29.

Table 27: Summary of Immunogenicity Results (GMT, GMR and SC rate) against homologues strains (by strain) for All Clinical Studies - FAS

Table 3-4: Summary of Immunogenicity Results (Geometric Mean Titer, Geometric Mean Ratio, and Seroconversion Rate) Against Homologous Strains (by Strain) for All Clinical Studies – FAS

	V118_05		V70_29		V70_50		V70P2 (PPS)		V70P6		V70_34	
	6 to <72 Months		6 to <72 Months		6 to <72 Months		6 to <36 Months		6 to <60 Months		6 to <36 Months	
	aQIV N=1481	Comp[a] N=1405	aTIV N=747	TIV-1 N=839	aTIV N=139	TIV-1 N=134	aTIV N=104	TIV-3 N=118	aTIV N=172	TIV-1 N=169	aTIV N=36	TIV-2 N=36
Strain: A/H1N1												
GMT Day 1	40.08 (32.3; 49.7)	39.49 (31.8; 49.1)	29 (25; 33)	24 (21; 28)	15 (12; 19)	15 (12; 19)	5.93 (5.01; 7)	6.4 (5.47; 7.49)	16 (12; 21)	16 (13; 21)	19 (9.95; 38)	49 (25; 95)
GMT Day 22/50[b]	996.40 (888.4; 1117.6)	522.50 (465.3; 586.7)	1519 (1372; 1683)	637 (577; 704)	705 (576; 863)	148 (120; 182)	195 (159; 240)	92 (76; 111)	1563 (1343; 1820)	1272 (1092; 1481)	1027 (706; 1493)	359 (246; 523)
GMR	24.96 (22.3; 28)	13.09 (11.7; 14.7)	57 (50; 65)	26 (23; 30)	47 (36; 61)	9.68 (7.45; 13)	33 (28; 38)	14 (12; 17)	101 (80; 126)	80 (64; 100)	42 (26; 69)	9.63 (5.95; 16)
SCR[c]	81.9 (79.7; 83.9)	73.7 (71.2; 76.1)	92.75 (90.65; 94.51)	83.67 (80.99; 86.11)	91 (84.4; 94.9)	72 (63.2; 79.1)	100 (97; 100)	86 (78; 91)	98 (95; 100)	98 (94; 99)	97 (85; 100)	72 (55; 86)
Strain: A/H3N2												
GMT Day 1	72.96 (58.1; 91.6)	70.38 (55.9; 88.5)	41 (36; 48)	42 (37; 49)	58 (41; 81)	57 (41; 80)	8.24 (6.25; 11)	8.79 (6.78; 11)	36 (26; 49)	40 (29; 55)	5.71 (4.5; 7.24)	5.71 (4.5; 7.24)
GMT Day 22/50[b]	1153.40 (1035.4; 1284.9)	674.01 (604.4; 751.6)	1909 (1791; 2035)	1016 (954; 1081)	1251 (1069; 1463)	446 (380; 523)	507 (412; 623)	195 (160; 237)	2084 (1789; 2427)	1030 (883; 1200)	963 (723; 1284)	199 (149; 265)
GMR	21.68 (19.5; 24.1)	12.67 (11.4; 14.1)	49 (43; 55)	25 (23; 28)	22 (17; 28)	7.72 (5.92; 10)	61 (50; 75)	22 (18; 27)	55 (42; 72)	27 (21; 35)	169 (122; 234)	35 (25; 48)
SCR[c]	78.4 (76.1; 80.6)	73.2 (70.7; 75.6)	96.39 (94.78; 97.60)	92.25 (90.23; 93.97)	78 (69.9; 84.3)	67 (58.5; 75)	98 (93; 100)	96 (90; 99)	96 (92; 99)	90 (84; 94)	100 (90; 100)	94 (81; 99)
Strain: B/Yamagata												
GMT Day 1	10.17 (9.0; 11.5)	10.12 (9.0; 11.4)	NA	NA	7.64 (6.74; 8.67)	6.96 (6.12; 7.91)	NA	NA	NA	NA	NA	NA
GMT Day 22/50[b]	198.89 (173.1; 228.5)	90.68 (78.8; 104.3)	NA	NA	74 (62; 89)	15 (13; 19)	NA	NA	NA	NA	NA	NA
GMR	18.08 (15.7; 20.8)	8.25 (7.2; 9.5)	NA	NA	10 (8.32; 12)	2.19 (1.8; 2.66)	NA	NA	NA	NA	NA	NA
SCR[c]	86.0 (84.1; 87.8)	64.7 (62.1; 67.3)	NA	NA	77 (69.41; 83.7)	20 (13.7; 27.9)	NA	NA	NA	NA	NA	NA

	V118_05		V70_29		V70_50		V70P2 (PPS)		V70P6		V70_34	
	6 to <72 Months		6 to <72 Months		6 to <72 Months		6 to <36 Months		6 to <60 Months		6 to <36 Months	
	aQIV N=1481	Comp[a] N=1405	aTIV N=747	TIV-1 N=839	aTIV N=139	TIV-1 N=134	aTIV N=104	TIV-3 N=118	aTIV N=172	TIV-1 N=169	aTIV N=36	TIV-2 N=36
Strain: B/Victoria												
GMT Day 1	10.45 (9.6; 11.4)	10.36 (9.5; 11.3)	9.97 (9.2; 11)	10 (9.49; 11)	NA	NA	5.42 (5.08; 5.77)	5.18 (4.88; 5.5)	5.86 (5.46; 6.29)	6.22 (5.79; 6.69)	8.53 (6.06; 12)	8.53 (6.06; 12)
GMT Day 22/50[b]	315.52 (287.5; 346.3)	138.82 (125.2; 153.9)	480 (441; 523)	164 (151; 178)	NA	NA	105 (88; 127)	20 (17; 24)	196 (164; 235)	66 (55; 79)	236 (167; 334)	45 (32; 64)
GMR	29.70 (26.9; 32.7)	13.28 (12.0; 14.7)	49 (45; 54)	17 (15; 18)	NA	NA	19 (16; 23)	3.95 (3.38; 4.62)	33 (28; 39)	10 (8.86; 12)	28 (20; 39)	5.31 (3.76; 7.5)
SCR[c]	91.0 (88.7; 93.0)	77.4 (74.2; 80.3)	97.46 (96.06; 98.46)	86.41 (83.91; 88.66)	NA	NA	99 (95;100)	33 (25; 42)	95 (91; 98)	76 (69; 82)	97 (85; 100)	47 (30; 65)

Source: CSR V118_05; Table 14.2.3.3.1.1; Table 14.2.3.3.1.4; Table 14.2.3.6.1.1, Table 14.2.3.6.1.4; CSR V70_29, Table 14.2.1.2.1, Table 14.2.1.2.2; CSR V70_50, Table 14.2.1.7; Table 14.2.1.8; CSR V70P2, Table 14.2.1.2, Table 14.2.1.3, CSR V70P6, Table 14.2.1.2.5, Table 14.2.1.3.5; CSR V70_34, Table 14.2.1.7.1, Table 14.2.1.11.1.

Abbreviations: aQIV = adjuvanted quadrivalent influenza vaccine; aTIV = adjuvanted trivalent influenza vaccine; comp = comparator vaccine in Study V118_05; CSR = clinical study report; FAS = full analysis set; GMR = geometric mean ratio; GMT = geometric mean titer; HI = hemagglutination inhibition; N = number of subjects with baseline and postbaseline serum samples, for individual time points by strain refer to the source table in the CSRs; SCR = seroconversion rate; TIV-1 = trivalent influenza vaccine 1; TIV-2 = trivalent influenza vaccine 2; TIV-3 = trivalent influenza vaccine 3.

[a] For Study V118_05; comparator vaccine included TIV-1 (Season 1) and QIV-1 (Season 2). B/Victoria results are presented for Season 2 only.

[b] For Studies V118_05 and V70_50, GMTs are pooled from Day 50 and Day 22 for vaccine naive and non-naive subjects, respectively.

[c] Seroconversion rate = percentage of subjects with either a prevaccination HI titer <1:10 and postvaccination HI titer ≥1:40 or with a prevaccination HI titer ≥1:10 and a minimum 4-fold increase in postvaccination HI antibody titer.

Note: Parentheses contain the 95% confidence intervals.

Table 28: GMT ratio at 21 Days after Last Vaccination Against Homologous Strains for All Clinical Studies - FAS

	V118_05		V70_29		V70_50		V70P2 (PPS)		V70P6		V70_34	
	6 to <72 Months		6 to <72 Months		6 to <72 Months		6 to <36 Months		6 to <60 Months		6 to <36 Months	
	aQIV N=1481	Comp[a] N=1405	aTIV N=747	TIV-1 N=839	aTIV N=139	TIV-1 N=134	aTIV N=104	TIV-3 N=118	aTIV N=172	TIV-1 N=169	aTIV N=36	TIV-2 N=36
Strain: A/H1N1												
GMTr	1.91 (**1.8**; 2.0)		2.38 (**2.02**; 2.81)		4.77 (**3.58**; 6.34)		2.13 (**1.61**; 2.83)		1.23 (0.98; 1.98)		2.86 (**1.67**; 4.9)	
Strain: A/H3N2												
GMTr	1.71 (**1.6**; 1.8)		1.88 (**1.7**; 2.08)		2.81 (**2.25**; 3.50)		2.6 (**1.96**; 3.46)		2.02 (**1.64**; 2.49)		4.85 (**3.23**; 7.28)	
Strain:B/Yamagata												
GMTr	2.19 (**2.0**; 2.4)		NA		4.82 (**3.72**; 6.24)		5.15 (**4.01**; 6.61)		2.97 (**2.33**; 3.81)		NA	
Strain:B/Victoria												
GMTr	2.27 (**2.0**; 2.6)		2.93 (**2.56**; 3.36)		NA		NA		NA		5.24 (**3.21**; 8.55)	

Source: CSR V118_05, Table 14.2.3.3.1.1, Table 14.2.3.3.1.4; CSR V70_29, Table 14.2.1.2.2; CSR V70_50, Table 14.2.1.8; CSR V70P2, Table 14.2.1.3; CSR V70P6, Table 14.2.1.3.5; CSR V70_34, Table 14.2.1.11.1.

Abbreviations: aQIV = adjuvanted quadrivalent influenza vaccine; aTIV = adjuvanted trivalent influenza vaccine; Comp = comparator vaccine in Study V118_05; CSR = clinical study report; FAS = full analysis set; GMT = Geometric mean titer; GMTr = geometric mean titer ratio; N = number of subjects with baseline and postbaseline serum samples, for individual time points by strain refer to the source table in the CSRs; NA = not applicable; PPS = per protocol set; TIV 1 = trivalent influenza vaccine 1; TIV-2 = trivalent influenza vaccine 2; TIV-3 = trivalent influenza vaccine 3.

[a] For Study V118_05, comparator vaccine included TIV-1 (Season 1) and QIV-1 (Season 2). B/Victoria results are presented for Season 2 only.

Note: Parentheses contain the 95% confidence intervals.

Bold = GMT ratio 95% confidence interval lower limit of >1.

Altogether, the supportive studies show that vaccination with aTIV produces a robust immune response which is higher compared to non-adjuvanted influenza vaccines.

2.5.4. Main studies (elderly indication)

The clinical development program to support licensure of aQIV in individuals ≥65 years of age is based on the results of the pivotal aQIV immunogenicity and safety study V118_20.

The data package also includes a key supportive aTIV study V70_27, 7 supportive aTIV studies, 7 aTIV revaccination studies, and 2 aTIV effectiveness studies. Additionally, the safety profile is supported by more than 20 years of aTIV postmarketing data.

Moreover, data from study V118_18 was submitted during the evaluation.

2.5.4.1. V118_20

Methods

Study V118_20 is a Phase 3, Randomized, Double-Blind, Controlled, Multicentre, Clinical Study to Evaluate Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Subunit Influenza Vaccine in Comparison With an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine and an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine Containing the Alternate B Strain, in Adults Aged 65 Years and Above.

Study Participants

This study enrolled 771 male and 1,007 female subjects ≥65 years old who were healthy or had co-morbidities, willing and able to participate in the study.

Inclusion Criteria

To participate in this study, subjects were required to meet all of the following inclusion criteria:

1. Males and females ≥65 year old who were healthy or had comorbidities.

2. Individuals who or whose legal representative(s) had voluntarily given written consent after the nature of the study had been explained according to local regulatory requirements, prior to study entry.
3. Ability to attend all scheduled visits and to comply with study procedures including Diary Card completion and follow-up (and responding to messages and telephone contact). A subject or legal representative was considered able to comply if the Investigator judged that the subject would complete the Diary Card when applicable, return for all the follow-up visits, and be available for telephone calls as scheduled in the study.

Exclusion Criteria

Subjects were ineligible to participate in this study if they met 1 or more of the following exclusion criteria:

1. History of behavioural or cognitive impairment or psychiatric condition that, in the opinion of the Investigator, may interfere with the subject's ability to participate in the study.
2. History of any medical condition considered an AESI.
3. Progressive or severe neurological disorder, seizure disorder, or history of Guillain-Barré Syndrome.
4. Hypersensitivity, including allergy, to any component of vaccines, medicinal products, or medical equipment whose use is foreseen in this study.
5. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws, including bleeding diathesis, or any other condition that may be associated with prolonged bleeding.
6. Abnormal function of the immune system resulting from:
    a. Clinical conditions affecting the immune system (e.g., HIV infection, agammaglobulinemia)
    b. Systemic administration of corticosteroids (PO/IV/IM) at a dosage equivalent to 20 mg/day of prednisone for more than 14 consecutive days within 90 days prior to informed consent
    c. Administration of antineoplastic and immunomodulating agents (e.g., TNF-α antagonists or anti-B cell antibodies) or radiotherapy within 1 year prior to informed consent
7. Receipt of immunoglobulins or any blood products within 180 days prior to informed consent.
8. Receipt of an investigational or nonregistered medicinal product within 30 days prior to informed consent or before completion of the safety follow-up period in another study, or who were unwilling to refuse participation in another clinical study at any time during the conduct of this study (note: concomitant participation in an observational study not involving drugs, vaccines, or medical devices, was acceptable).
9. Study personnel or immediate family members (brother, sister, child, parent) or the spouse of personnel with direct involvement in the study.
10. Receipt of any influenza vaccine within 6 months prior to enrollment in this study or planned to receive influenza vaccine prior to the Day 22 blood collection.

11. Receipt of any inactivated non-influenza vaccine within 14 days or live-attenuated vaccine within 28 days prior to enrollment in this study or planned to receive any other non-influenza vaccine within 28 days of study vaccination.
12. Fever at the time of screening, defined as oral temperature ≥38.0°C (≥100.4°F). Enrollment could have been considered if fever was absent for 72 hours.
13. Signs or symptoms of acute infection at the time of screening. Enrollment could have been deferred if signs and symptoms were absent for 72 hours.
14. Fatal prognosis of an underlying medical condition (<12 months life expectancy).
15. Any other clinical condition that, in the opinion of the Investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

Treatments

There were three treatment groups:

1) **aQIV group (candidate vaccine):** A 0.5 mL dose of aQIV contains nominally 15 mcg of HA of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 mcg of HA in the vaccine. The strains used in this study were compliant with recommendations by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season (WHO 2017) for quadrivalent vaccines: A/ Michigan/45/2015 (H1N1)-like virus; A/ Hong Kong/4801/2014 (H3N2)-like virus; B/ Phuket/3073/2013-like virus (Yamagata lineage); B/ Brisbane/60/2008-like virus (Victoria lineage).
2) **aTIV-1 group:** A 0.5 mL dose of aTIV-1 contains nominally 15 mcg of HA of each of the 2 influenza type A strains and the recommended influenza type B strain for a total of 45 mcg of HA in the vaccine. The strains used in this study were compliant with recommendations by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season (WHO 2017) for trivalent vaccines: A/ Michigan/45/2015 (H1N1)-like virus; A/ Hong Kong/4801/2014 (H3N2)-like virus; B/ Brisbane/60/2008-like virus (Victoria lineage).
3) **aTIV-2 group:** A 0.5-mL dose of aTIV-2 contains nominally 15 mcg of HA of each of the 2 influenza type A strains and 1 influenza type B s train for a total of 45 mcg of HA in the vaccine. The influenza A strains used in the study were compliant with recommendations by the World Health Organization for the 2017-2018 Northern Hemisphere influenza season (WHO 2017) for trivalent vaccines. The influenza B strain included in this vaccine was the second influenza B strain recommended for inclusion in quadrivalent vaccines (i.e., the alternate B strain): A/ Michigan/45/2015 (H1N1)-like virus; A/ Hong Kong/4801/2014 (H3N2)-like virus; B/ Phuket/3073/2013-like virus (Yamagata lineage).

Objectives

Study Objectives:

Co-Primary Immunogenicity Objectives:

1. To demonstrate that vaccination with aQIV elicits an immune response that is not inferior to that of an aTIV containing the same virus strains as the licensed adjuvanted influenza vaccine (FLUAD, aTIV-1), and an aTIV containing the alternate B strain (aTIV-2) among adults ≥65 years of age.

2. To assess the immunogenicity of aQIV in adults ≥65 years of age based on the CBER (Center for Biologics Evaluation and Research) recommendations.

Secondary Immunogenicity Objectives:

The secondary immunogenicity objectives of the study were to assess the following, among adults aged ≥65 years:

1. To characterize the immunogenicity of aQIV, the aTIV-1 containing the same virus strains as the licensed adjuvanted trivalent influenza vaccine, and the aTIV-2 containing the alternate B strain, by hemagglutination inhibition (HI).
2. To demonstrate the immunological superiority of aQIV compared to aTIV-1 and aTIV-2 for the B strain that is not included in each TIV vaccine separately.

Secondary Safety Objective:

1. To assess safety and tolerability of aQIV, aTIV-1, and aTIV-2 among adults >65 years of age.

Exploratory Immunogenicity Objectives:

1. To explore the association between HI immune response after administration of aQIV or the aTIV-1, containing the same virus strains as the licensed adjuvanted trivalent influenza vaccine, and the aTIV-2 containing the alternate B strain by baseline characteristics.
2. Characterization of the immunogenicity of aQIV using other immunological assays (e.g., virus neutralization [MN] or anti-neuraminidase antibody assays may be performed).

Note: Additional immunogenicity testing (e.g., virus neutralization [microneutralization]) was not performed as part of this study; therefore, exploratory immunogenicity objective #2 was not assessed. All study objectives were performed using homologous strains.

Outcomes/endpoints

Co-Primary Immunogenicity Endpoints

The immunogenicity of study vaccines was assessed 21 days (i.e., on Day 22) after vaccine administration by measuring the HI antibody titers to the 4 virus homologous strains included in the investigational vaccine.

The noninferiority of aQIV compared to aTIV-1 and to aTIV-2 was assessed for the 8 co-primary endpoints of HI geometric mean titer (GMT) and seroconversion rate (SCR) for each virus strain included in the vaccines as follows:

- GMT ratio* for the A/H1N1 strain
- GMT ratio for the A/H3N2 strain
- GMT ratio for the B strain (Yamagata lineage)
- GMT ratio for the B strain (Victoria lineage)
- Difference between the SCR** for the A/H1N1 strain
- Difference between the SCR for the A/H3N2 strain
- Difference between the SCR for the B strain (Yamagata lineage)
- Difference between the SCR for the B strain (Victoria lineage)

**The GMT ratio was defined as the geometric mean of the postvaccination (Day 22) HI titer for aTIV-1 (or aTIV-2) over the geometric mean of postvaccination (Day 22) HI titer for aQIV.*

***The SCR was defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40 or a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer.*

Immunogenicity results obtained from aTIV-1 and aTIV-2 for both A/H1N1 and A/H3N2 strains were pooled for comparison with aQIV.

The second co-primary immunogenicity objective for aQIV was assessed 21 days after vaccine administration by applying CBER criteria for the elderly population for each of the 4 strains included in aQIV:

- Percentage of subjects achieving seroconversion for HI antibody
- Percentage of subjects achieving an HI antibody titer ≥1:40

Success Criteria for Co-Primary Objectives

To Demonstrate Noninferiority

aQIV was considered to be noninferior to aTIV-1, containing the same virus strains as the licensed adjuvanted trivalent influenza vaccine, and aTIV-2, containing the alternate B strain if, for each of the 4 strains, the following statistical criteria were met:

- The upper bound of the two-sided 95% confidence interval (CI) for the ratio of the GMTs did **not** exceed 1.5. The GMT ratio was calculated as GMTaTIV/GMTaQIV.
- The upper bound of the two-sided 95% CI for the difference between the SCRs did **not** exceed 10%. The difference in SCRs was calculated as SCRaTIV–SCRaQIV.

To Demonstrate Sufficiency of the Immune Response According to CBER Criteria

The sufficiency of immune response after aQIV was assessed as measured by percentage of subjects achieving seroconversion and HI titer ≥1:40 at Day 22 according to the criteria presented in the CBER Guidance for Licensure of Seasonal Inactivated Influenza Vaccines (CBER FDA 2007), namely:

- The lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should have met or exceeded 30%;
- The lower bound of the two-sided 95% CI for the percentage of subjects achieving a postvaccination HI antibody titer ≥1:40 should have met or exceeded 60%.

The statistical evaluation consisted of the observed proportion together with the lower bound of the corresponding two-sided 95% CI per strain. No adjustment for type I error for multiplicity was made.

Secondary Immunogenicity Endpoints

Secondary immunogenicity endpoints included:

For Secondary Objective 1, the measures of immunogenicity of aQIV, aTIV-1, and aTIV-2, as determined by the HI assay against homologous strains at Day 1 and 22 (unless indicated otherwise), included the following:

- GMT: Geometric mean of HI titers on Day 1 (prevaccination) and Day 22 (postvaccination);

- Geometric mean ratio (GMR*): the geometric mean of the fold increase of postvaccination HI titer over the prevaccination HI titer (Day 22/Day 1);
- The percentage of subjects with HI titer ≥1:40 at Day 1 and Day 22;
- SCR: the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a ≥4-fold increase in postvaccination titer on Day 22.

**GMR was defined as the geometric mean of the fold increases of postvaccination antibody titer over the prevaccination antibody titer.*

For each treatment group and strain, summary tables were presented for GMT and 95% CIs, percentage of subjects with a titer ≥1:40 (number and percentage of subjects) at Day 1 and Day 22 SCR (number and percentage of subjects at Day 22) and GMR (mean and 95% CIs).

For Secondary Objective 2, the immunologic superiority of HI antibody responses for the alternate B strain (e.g., the influenza B strain included in the aQIV but not in the aTIV formulation) were assessed for each aTIV separately, using the endpoints of the ratio of HI GMT and the difference of SCR for each B virus strain 21 days after vaccination.

- For comparisons between aQIV and aTIV-1, the alternate B strain was B/Yamagata;
- For comparisons between aQIV and aTIV-2, the alternate B strain was B/Victoria.

Success Criteria for Superiority Demonstration (Secondary Objective 2)

Superiority was declared if the upper limit of the two-sided 95% CI for the difference in seroconversion rates (SCRaTIV–SCRaQIV) was <0, and the upper limit of the two-sided 95% CI for the GMT ratio (GMTaTIV/GMTaQIV) was <1 for both B strains.

Exploratory Immunogenicity Endpoints

Analyses of the exploratory immunogenicity endpoints for homologous strains (namely postvaccination GMTs and SCR) were performed with adjustment for covariates including prevaccination titer, vaccination history, age, and gender to evaluate the contribution of these factors to variations in the immune response. The covariate adjustment was performed with all of the specified covariates in the GLM.

No other exploratory analyses were performed.

Sample size

Approximately 1,778 were planned to be randomized in a 2:1:1 ratio (aQIV:aTIV-1:aTIV-2). This study was powered to achieve 80% power to demonstrate noninferiority over 8 co-primary endpoints, SCRs for 4 strains, and GMT for 4 strains using a 1-sided alpha of 0.025 for each comparison. No adjustment for multiple comparisons was made.

For comparisons of SCR, a noninferiority margin of 10% (aTIV–aQIV) was employed. It was assumed that the SCRs for A-H1N1, A-H3N2, and B strains for TIV were 73%, 73%, and 40%, respectively. These estimates were based on the estimated SCR rates of historical data, namely study Protocol V70_27. It was assumed that there was no difference in terms of SCR between aQIV and aTIV for all strains. For comparison of the GMT ratio, a noninferiority of 1.5 (aTIV/aQIV) was employed. It was assumed that there was no difference between aQIV and aTIV (i.e., a ratio of 1) and that the standard deviation of log (titer) was 1.2.

Under these assumptions, the number of subjects in the FAS Immunogenicity equalled 800 in the aQIV group and 400 subjects in each aTIV group, providing 800 subjects and 800 subjects receiving aQIV and aTIV, respectively, for comparisons of A strains, and 800 subjects and 400 subjects receiving aQIV and aTIV, respectively, for comparisons of B strains. This provided a total FAS Immunogenicity of 1,600. These numbers provided 99.45% power to detect differences in SCR for each A strain and 91.29 % power for each B strain, providing overall 82.42% power for the 4 SCR tests.

For GMT ratio tests, each A strain test had 100% power and each B strain test had 99.98% power, providing 99.96% power for the 4 GMT ratio tests and, consequently, 82.39% power for the 8 co-primary endpoints. A total of N=1778 subjects were to be recruited considering a 10% drop-out rate and 1600 subjects for FAS Immunogenicity requirement.

Randomisation

An Interactive Response Technology (IRT) system was used for subject randomization, which assigned a unique subject identification number. Subjects who provided informed consent and who met all criteria for enrollment were randomly assigned in a 2:1:1 ratio to receive aQIV, aTIV-1, or aTIV-2.

Blinding (masking)

This was a double-blind study. There were no visible differences between the investigational aQIV vaccine and the 2 comparator aTIV vaccines. Vaccines were selected and administered according to the Pack ID assigned to the subjects by the IRT system. Neither the subject nor any of the investigative staff involved in administering the vaccines or clinical evaluation of the subject were aware of the vaccine administered.

No unblinding occurred during the study. The Protocol had prespecified unblinding procedures for the handling of medical emergency or accidental unblinding. The unblinding should only have been performed when knowledge of the assigned treatment would have affected a subject's management. Except in the case of medical necessity, a subject's treatment should not have been unblinded without the approval of the Sponsor.

Statistical methods

Analysis Sets

There were 5 analysis sets defined for the study analyses.

All Enrolled Set: The All Enrolled Set included all subjects who provided informed consent, received a subject identification number, and provided demographic and/or baseline screening information, regardless of randomization and treatment status in the study.

Exposed Set: The Exposed Set included all subjects in the All Enrolled Set who received study vaccination.

Full Analysis Set Immunogenicity: The Full Analysis Set (FAS) Immunogenicity included all subjects in the All Enrolled Set who were randomized, received at least 1 study vaccination, and provided immunogenicity data at Day 1 and Day 22.

In the case of a vaccination error, subjects in the FAS Immunogenicity were analyzed "as randomized" (i.e., according to the vaccine the subject was randomized to receive, which may have differed from the vaccine the subject actually received). If a subject was unblinded during the study, that subject was included in the FAS Immunogenicity.

Per Protocol Set Immunogenicity: The Per Protocol Set (PPS) Immunogenicity comprised all subjects in the FAS Immunogenicity who did not have any major PDs that were assessed as potentially impacting on immunogenicity results. Examples of subjects excluded from the PPS due to other reasons than major protocol deviations were: subjects who withdrew informed consent, subjects who had RT-PCR–confirmed ILI before Day 22 (as documented by the central laboratory), and unblinding of vaccine assignment (except in the case of a SUSAR).

Safety Set: The Safety Set included all subjects in the Exposed Set who received at least 1 dose or a partial dose of study vaccine and provided any evaluable follow-up safety data

– **Solicited Safety Set:** All subjects in the Exposed Set with any solicited AE data.

– **Unsolicited Safety Set:** All subjects in the Exposed Set with unsolicited AE data.

– **Overall Safety Set:** All subjects who were in the solicited safety set or in the unsolicited safety set. In case of vaccination error, subjects were analyzed as "treated" (i.e., according to the vaccine a subject received rather than the vaccine to which the subject was randomized).

If a subject received the correct study vaccine (dose, batch) from another ongoing study at the site, the subject's safety data were included in the safety analysis. If a subject was unblinded during the study, he/she was included in all safety sets.

Immunogenicity Data Analysis

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

Co-primary immunogenicity endpoints of GMT and SCR for each virus strain contained in the vaccine was assessed for subjects ≥65 years overall. For A-H1N1 and A-H3N2 strains, the two aTIV treatment groups were pooled.

Primary analysis was performed for subjects ≥65 years using the Per Protocol Set. The difference in SCRs was presented with exact 95% (CIs). Miettinen and Nurminen method was used if convergence issues (Miettinen and Nurminen 1985). Each of the 4 strains was analyzed separately.

To determine the GMT ratio (adjusted analysis), a general linear model (GLM) was fitted on log transformed (base ten) postvaccination HI titer as the outcome variable and terms for covariates: vaccine treatment, prevaccination HI titer, age stratum, gender, vaccination history, age-by vaccine interaction and study site. Potential covariate interaction effects were also examined in the fit of the GLM. From the model, an adjusted difference in least square means (on the log scale) was produced with 95% confidence limits. The estimated difference and the confidence limits were back transformed to obtain an adjusted GMT ratio with 95% confidence limits. Each of the 4 strains was analyzed separately. The adjusted GMT ratio was the result for which the noninferiority assessment of the HI GMT co-primary endpoint was based on.

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

Binary data (i.e., percentages of subjects with seroconversion and with titer ≥1:40) were summarized for each group using crude estimates and reported together with two-sided exact 95% CIs. No multiplicity adjustment to the CI levels was implemented.

Missing immunogenicity values were considered missing completely at random and, therefore, did not contain information that affected the result of the analysis (i.e., not informative).

Therefore, imputation methods were not used.

The PPS was used for the primary/secondary immunogenicity noninferiority analyses, as well as supplementary analyses, and FAS was used for secondary superiority analysis. Duplicate tables of primary and secondary immunogenicity analyses have been produced based on the FAS/PPS immunogenicity if there was >1% difference in the total number of subjects between the PPS and the FAS Immunogenicity.

Subgroup Analysis

Additional subgroup analyses were conducted for both safety and immunogenicity assessments, based on following subgroups:

- Age at enrollment (≥65 to 74, ≥75 to 84, and ≥85 years)
- Gender
- Race
- Previous influenza vaccination in the past 5 years (yes/no)
- Comorbidity/risk (yes/no, defined as assessment score <50 or ≥50 based on scale described in Section 5.1.2 of the Protocol (Appendix 16.1.1)

Results

Participant flow

In total 1,778 subjects were enrolled and randomized into the study, with 1,776 (99.9%) subjects in the Exposed Set receiving 1 vaccination of aQIV, aTIV-1, or aTIV-2. The total number of subjects who completed the full study was 1,760 (99.0%).

Figure 2: subject disposition

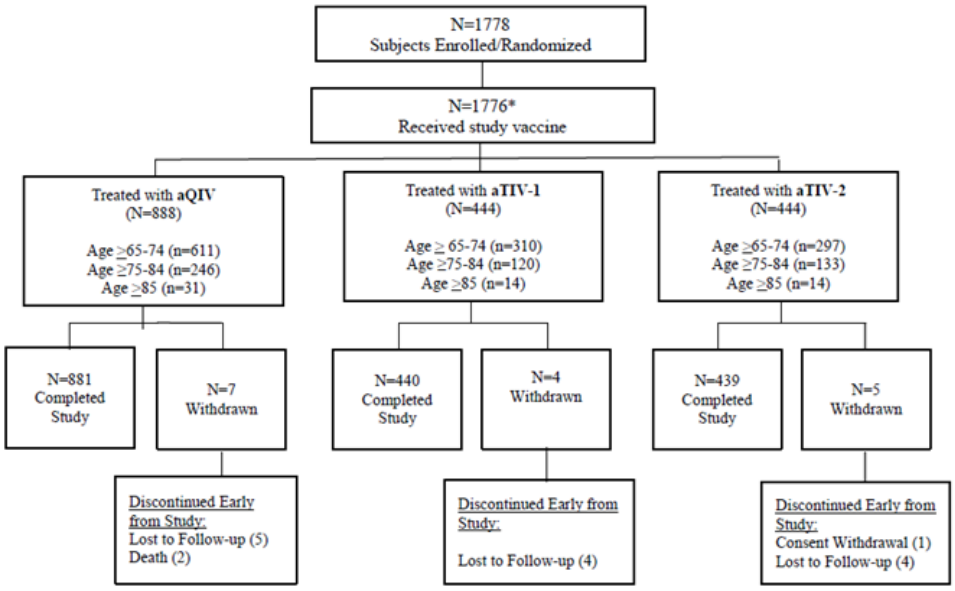


Figure 2. Of the total of 1778 subjects enrolled and randomized, a total of 1776 subjects were given study vaccination. A total of 1760 subjects completed the study. Reasons for early discontinuation from the study included withdrawal of consent (n=1), lost to follow-up (n=13), and death unrelated to the study vaccine (n=2).
* Two subjects, 1170070 and 1170071, had consent withdrawn after randomization and did not receive study vaccine.
Source: Table 14.1.1.2, Listing 16.2.1.1

In total, 1,778 subjects were enrolled in the study. Two randomized subjects did not receive study vaccination and were excluded from the Exposed Set. Overall, 1,776 subjects received the study vaccination. Five subjects (1 subject from aQIV group, 1 subject from aTIV-1 group, and 3 subjects from aTIV-2 group) were early terminated prior to Day 22. One subject from aQIV group did not provide evaluable blood sample at Day 22. These 6 subjects were excluded from the FAS Immunogenicity. In total, 1770 subjects were included in the FAS.

Overall, 29 subjects were excluded from the PPS (14 subjects in the aQIV group; 7 subjects in aTIV-1; and 8 subjects in aTIV-2).

Overall, the main reasons for exclusion of subjects from the PPS were balanced between study groups.

Recruitment

Study V118_20 was conducted in the US during the 2017-2018 Northern Hemisphere influenza season and enrolled a total of 1,778 male and female subjects ≥65 years of age.

Subjects were recruited before the start of the influenza season, in 2017, and had two stages of study participation: Treatment Period (Day 1 through Day 22) and Follow-up Period (Day 23 through Day 181). Thus, subjects were followed-up during 6 months after vaccine administration.

Conduct of the study

There were no amendments made to the protocol. No unblinding occurred during the study. Overall, there were 88 (4.9%) subjects who had at least 1 major protocol deviation. The most common major protocol deviations were associated with missed study visits or visits outside of the protocol-specified time intervals (1.9%).

Baseline data

The median overall age of subjects was 71 years; the minimum age in each group was 65 years, and the maximum was 90 to 97 years. A majority of subjects (56.6%) were female vs. 43.4% male.

The enrolled population was predominantly white race (91.6%) and non-Hispanic or Latino ethnicity (92.5%). Mean weights were 83.24 kg to 84.24 kg across study groups. The median BMI was high in all study groups, ranging from 28.62 to 28.96. Most subjects (86.7%) had previous influenza vaccination.

Overall, based on the Risk Scores, the enrolled population was considered to be low risk for hospitalization due to pneumonia or influenza and death from any cause; however, subjects ≥75 years of age tended to be higher risk for influenza-related hospitalizations and death from any cause.

There were no other notable differences observed in the baseline characteristics and demographics across vaccine groups in the overall enrolled population.

The distribution of demographic and baseline characteristics by vaccine groups in the FAS and PPS analysis sets were generally similar compared with the Enrolled Set. Similar to the enrolled set, subjects in the FAS and PPS who were ≥75 years tended to be at higher risk for influenza-related hospitalization and death from any cause; and most subjects had previous influenza vaccination.

Table 29: summary of demographics and baseline characteristics – as randomised by age at enrolment (all enrolled set)

	aQIV vaccine (N=889)	aTIV-1 vaccine (N=445)	aTIV-2 vaccine (N=444)	Total (N=1778)
Age (years)				
N	889	445	444	1778
Mean (SD)	72.4 (5.54)	72.4 (5.60)	72.6 (5.46)	72.5 (5.53)
Median	71.0	71.0	72.0	71.0
Sex, n (%)				
Male	372 (41.8)	196 (44.0)	203 (45.7)	771 (43.4)
Female	517 (58.2)	249 (56.0)	241 (54.3)	1007 (56.6)
Race, n (%)				
White	814 (91.6)	403 (90.6)	411 (92.6)	1628 (91.6)
Black or African American	59 (6.6)	37 (8.3)	29 (6.5)	125 (7.0)
Asian	9 (1.0)	2 (0.4)	1 (0.2)	12 (0.7)
Native Hawaiian or Pacific Islander	1 (0.1)	1 (0.2)	0	2 (0.1)
American Indian or Alaska Native	5 (0.6)	0	2 (0.5)	7 (0.4)
Other	1 (0.1)	2 (0.4)	1 (0.2)	4 (0.2)
Ethnicity, n (%)				
Hispanic or Latino	59 (6.6)	37 (8.3)	31 (7.0)	127 (7.1)
Not Hispanic or Latino	827 (93.0)	408 (91.7)	410 (92.3)	1645 (92.5)
Not Reported	2 (0.2)	0	2 (0.5)	4 (0.2)
Unknown	1 (0.1)	0	1 (0.2)	2 (0.1)

	aQIV vaccine (N=889)	aTIV-1 vaccine (N=445)	aTIV-2 vaccine (N=444)	Total (N=1778)
Height (cm)				
N	885	442	444	1771
Mean (SD)	167.54 (9.350)	167.92 (10.535)	168.38 (10.646)	167.84 (9.990)
Median	167.40	167.64	168.27	167.64
Weight (kg)				
N	885	442	444	1771
Mean (SD)	83.24 (19.064)	84.18 (18.963)	84.24 (17.825)	83.73 (18.731)
Median	80.56	82.44	82.48	81.80
BMI (kg/m^2)				
N	885	442	444	1771
Mean (SD)	29.60 (6.157)	29.79 (5.858)	29.69 (5.647)	29.67 (5.956)
Median	28.62	28.96	28.93	28.86
Influenza Vaccination History, n (%)				
Yes	760 (85.5)	380 (85.4)	401 (90.3)	1541 (86.7)
No	129 (14.5)	65 (14.6)	43 (9.7)	237 (13.3)
Total Risk Score (Comorbidity)				
N	889	445	444	1778
Mean (SD)	46.0 (33.50)	44.6 (30.25)	46.5 (34.15)	45.8 (32.88)
Median	38.0	38.0	39.0	39.0

Abbreviations: BMI=body mass index; max=maximum; min=minimum; SD=standard deviation.

Note 1: aQIV: MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-1: Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-2: MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain.

Note 2: Percentages were based on the number of subjects in Randomized Set with non-missing data within vaccine group for each age cohort.

Note 3: Age was calculated as Round (Date of Visit 1 – Date of Birth + 1)/365.25.

Note 4: BMI was calculated as Weight (kg)/[Height (m)]^2. Weight data collected on Day 0 vaccination was used for calculation.

Note 5: Subjects who refused to identify their ethnicity were coded as not reported. Subjects who did not know their ethnic background were coded as unknown.

Note 6: As randomized: according to the vaccine a subject was designated to receive, which may have been different from the vaccine the subject actually received.

Source: Table 14.1.1.3.1

Numbers analysed

Overall, 1,778 subjects were enrolled and randomized into the study, with 1,776 (99.9%) subjects receiving study vaccination of aQIV, aTIV-1, or aTIV-2, with 1,770 (99.6%) subjects included in the immunogenicity Full Analysis Set (FAS) and 1,741 (97.9%) subjects included in the immunogenicity Per Protocol Set (PPS).

In the ≥65 to 74 year age cohort, 1,220 subjects were enrolled and randomized, with 1,218 (99.8%) subjects receiving 1 vaccination of aQIV, aTIV, or aTIV-2, and 1,213 (99.4%) subjects included in the immunogenicity FAS and 1198 (98.2%) subjects included in the immunogenicity PPS.

In the ≥75 to 84 year age cohort, 499 subjects were enrolled and randomized, with 499 (100%) subjects receiving 1 vaccination of aQIV, aTIV, or aTIV-2, and 498 (99.8%) subjects included in the immunogenicity FAS and 484 (97.0%) subjects included in the immunogenicity PPS.

In the ≥85 year age cohort, 59 subjects were enrolled and randomized, with 59 (100%) receiving 1 vaccination of aQIV, aTIV, or aTIV-2, and 59 (100%) subjects included in both immunogenicity FAS and PPS.

Outcomes

Analysis of immunogenicity was performed on the PPS Immunogenicity (primary analysis) and on the FAS Immunogenicity, as more than 1% of the vaccinated subjects with postvaccination immunological results were eliminated from the PPS for immunogenicity. The primary analysis of immunological superiority for the B strains (secondary objective 2) was based on the FAS with supportive analysis performed on the PPS.

Immunogenicity was assessed by the HI assay conducted on serum samples collected before vaccination on Day 1 and on Day 22 by titrating antibodies against homologous influenza strains. Homologous strains are antigenically similar to the strains in the vaccine. Testing of samples was performed with Day 1 and Day 22 sera tested in the same assay run.

The WHO recommended homologous strains used in the assessment of antigenicity were A/ Singapore/GP1908/2015 IVR-180 (H1N1)-like; A/ Hong Kong/4801/X-263B (H3N2)-like, B/ Brisbane/9/2014-like (Yamagata lineage) and B/ Brisbane/60/2008-like (Victoria lineage).

Additional immunogenicity testing (e.g., MN) was not performed as part of this study.

Testing was conducted by Seqirus-designated qualified laboratory personnel who were blinded to the treatment assignment and the visit.

<u>First Co-primary Immunogenicity Objective: Non-inferiority of aQIV vs. aTIV Comparators (aTIV-1 and aTIV-2)</u>

Geometric Mean Titer Ratios

Table 31 presents the postvaccination HI antibody GMTs and analyses of noninferiority of aQIV relative to aTIV for each strain 22 days postvaccination in adults ≥65 years.

The prespecified noninferiority criteria for the adjusted GMT ratio were met for all 4 homologous strains. The upper bounds of the two-sided 95% confidence interval for the adjusted GMT ratios (aTIV/aQIV) did not exceed 1.5 (A-H1N1=1.27, A-H3N2=1.09, B-Yamagata=1.08 and B-Victoria=1.08).

Table 30: Analyses of Non-inferiority of aQIV Relative to aTIVs as Measured by HI GMT ratios for each strain 22 days post-vaccination in adults aged ⩾65 years (Per-Protocol Set)

	Study groups					
Strain	**aQIV**	**aTIV-1**	**aTIV-2**	**aTIV pooled**	**GMT ratio[a] (aTIV/aQIV) and 95% CI**	**Noninferiority[b] met?**
N	872	436	433	869		
A/H1N1	65.01	--	--	75.16	1.16 (1.05, **1.27**)	Yes
A/H3N2	294.91	--	--	293.31	0.99 (0.90, **1.09**)	Yes
B/Yamagata	24.67	--	24.30		0.99 (0.90, **1.08**)	Yes
B/Victoria	30.78	30.13	--		0.98 (0.89, **1.08**)	Yes

Abbreviations: CI=confidence interval; GMT=geometric mean titer; HI=hemagglutinin inhibition.
Note 1: aQIV: MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-1: Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-2: MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain;
Note 2: GMT is the Geometric Mean of HI titers on Day 22; the GMT Ratio was defined as the geometric mean of the postvaccination (Day 22) HI titer for aTIV-1 and/or aTIV-2 divided by the geometric mean of postvaccination (Day 22) HI titer for aQIV.
Note 3: N is the number of subjects with non-missing HI titer results at both prevaccination and postvaccination; Individual HI titers that were recorded as '<10' were taken as equal to 5.
Note 4: *Adjusted Model: Log-Transformed Postvaccination HI Titer = Vaccine Group [3 vaccines] + Age Group [≥65-74, ≥75-84, and ≥85 years] + Sex [male, female] + Vaccination History [y/n] + Log-transformed Prevaccination HI Titer + Site.
Note: Confidence intervals for the GMT ratio were calculated based on the normality assumption of log titers. aTIV-1 and aTIV-2 vaccine groups were pooled for the analysis of A-H1N1 and A-H3N2 strains. For B/Victoria TIV=aTIV-1, for B/Yamagata TIV=TIV-2.
a GMT Ratio=aTIV/aQIV.
b Noninferiority criterion for the GMT ratio: the upper bound of the two-sided 95% CI on the ratio of GMT (aTIV/aQIV) should not have exceeded 1.5.
Source: Table 14.2.1.1.1

Seroconversion Rate Difference

The SCR was defined as the proportion of subjects with either a titer of <1:10 before vaccination achieving a HI antibody titer of ≥1:40 after vaccination, or with a HI titer of ≥1:10 before vaccination achieving a 4-fold or greater increase in HI titer after vaccination.

The table below presents seroconversion rates and analyses of noninferiority of aQIV relative to aTIVs for each strain 22 days postvaccination in adults ≥65 years in the PPS.

The prespecified noninferiority criteria for the difference in the SCR between aTIV and aQIV were met for all 4 homologous strains. The upper bounds of the 95% CI of the intergroup difference for SCR (aTIV minus aQIV) did not exceed the noninferiority margin of 10% for all 4 strains (A-H1N1=7.76, A-H3N2=4.96, B-Yamagata=3.27, and B-Victoria=2.55).

Table 31: Non-inferiority of aQIV Relative to aTIVs as Measured by HI SC rates for each strain 22 days post-vaccination in adults aged ⩾65 years (Per-Protocol Set)

	Seroconversion rate[a] %			SCR Difference[b]	95% CI for SCR Difference[c]		Met both predefined non-inferiority criteria?
	aQIV	aTIV-1	aTIV-2	aTIV minus aQIV %	Lower 95%	Upper 95%	
N	**872**	**436**	**433**				
A-H1N1	35.21 (32, 38.5)	39.45 (34.8, 44.2)	37.41 (32.8, 4.2)	3.23	-1.30	**7.76**	Yes
A-H3N2	39.33 (36.1, 42.7)	39.70 (36.4, 43.0)	37.18 (32.6, 41.9)	0.37	-4.23	**4.96**	Yes
B-Yamagata	16.4 (14.0, 19.0)	--	15.47 (12.2, 19.2)	-0.93	-5.13	**3.27**	Yes
B-Victoria	13.42 (11.2, 15.9)	12.16 (9.24, 15.6)	--	-1.26	-5.07	**2.55**	Yes

Abbreviations: CI=confidence interval; GMT=geometric mean titer; HI=hemagglutinin inhibition; SCR=seroconversion rate.
Note 1: aQIV: MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-1: Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-2: MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain.
Note 2: The 95% CIs for SCR were the exact confidence intervals based upon the binomial distribution.
Note 3: The asymptotic 95% CIs for the difference in SCRs between aTIV and aQIV.
Note 4: aTIV-1 and aTIV-2 vaccine groups are pooled for the analysis of A-H1N1 and A-H3N2 strains. For B/Victoria TIV=aTIV-1, for B/Yamagata TIV=aTIV-2.

Second Co-Primary Immunogenicity Objective: Adequate Immunogenicity According to CBER Criteria

The second co-primary objective was to demonstrate adequate immunogenicity based on CBER criteria as measured by the percentage of subjects achieving seroconversion for HI antibodies and percentage of subjects achieving an HI antibody titer ≥1:40.

Success criteria was met if the lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody met or exceeded 30% AND the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 met and exceeded 60% (CBER Guidance Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines) (FDA 2007).

Percentage of Subjects Achieving Seroconversion

As presented in Table 11 for the PPS, the lower limit of the two-sided 95% CI for the proportion of subjects achieving seroconversion for HI antibody for A-H1NI and A-H3N2 strains were above 30%, but were below 30% for both B strains (B-Yamagata and B-Victoria). Therefore, the CBER success criteria for seroconversion were met for A strains, but not for B strains. Seroconversion rates for B strains in the aTIV-1 and aTIV-2 B groups were similar (lower limits of the 95% CI below 30%).

Percentage of Subjects Achieving Hemagglutination Inhibition ≥1:40

The lower limit of the two-sided 95% CI for the proportion of subjects achieving an HI antibody titer ≥1:40 for A-H1N1 and A-H3N2 strains were above 60%, but were below 60% for both B strains; therefore, the CBER success criteria for proportion of subjects with HI titer ≥1:40 were met for A strains,

but not for B strains. The proportion of subjects with HI titer ≥1:40 against B strains in the aTIV-1 and aTIV-2 groups were similar (lower limits of the 95% CI below 60%).

Table 32: Immunogenicity as Measured by Percentages of subjects with HI titer >1:40 and seroconversion rate to each homologous strain 22 days after vaccination (PPS)

	aQIV	aTIV-1/aTIV-2[a]
	n=872	n=869
A-H1N1		
Day 22 Post-V % HI titer ≥1:40 (95% CI)	69.38 (66.2, 72.43)	70.31 (67.15, 73.33)
SCR (%) (95% CI)	35.21 (32.03, 38.48)	38.43 (35.19, 41.76)
A-H3N2		
Day 22 Post-V % HI titer ≥1:40 (95% CI)	93.92 (92.12, 95.41)	94.82 (93.13, 96.2)
SCR (%) (95% CI)	39.33 (36.08, 42.67)	39.70 (36.43, 43.04)
B-Yamagata		
Day 22 Post-V % HI titer ≥1:40 (95% CI)	32.80 (29.69, 36.03)	36.95 (32.39, 41.69)
SCR (%) (95% CI)	16.40 (14.0, 19.03)	15.47 (12.20, 19.23)
B-Victoria		
Day 22 Post-V % HI titer ≥1:40 (95% CI)	38.19 (34.95, 41.51)	36.93 (32.38, 41.65)
SCR (%) (95% CI)[b]	13.42 (11.22, 15.86)	12.16 (9.24, 15.60)

Abbreviations: CI=confidence interval; HI=hemagglutination inhibition; Post-V=postvaccination; SCR=seroconversion rate.

Note 1: aQIV: MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-1: Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-2: MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain.

Note 2: The SCR was defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40 or a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer.

Note 3: Success criteria was met if the lower limit of the two-sided 95% CI for the percentage of subjects achieving SCR for HI antibody met or exceeded ≥30% AND the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 was ≥60%.

a aTIV-1 and aTIV-2 vaccine groups were pooled for the analysis of A-H1N1 and A-H3N2 strains. For B-Victoria TIV=aTIV-1, for B-Yamagata TIV=aTIV-2.

Source: Table 14.2.2.2, Table 14.2.2.1.1

Secondary Immunogenicity Endpoints

The secondary immunogenicity objective was to demonstrate the immunological superiority of aQIV compared to aTIV-1 and aTIV-2 for the B strain that was not included in each TIV vaccine, as measured by SCR difference and GMT ratio, and to further characterize the immunogenicity of study vaccines, as measured by HI assay.

- Immunologic Superiority of aQIV Relative to aTIV for the Alternate B Strain

Superiority of aQIV vs. aTIV-1 and aTIV-2 for the alternate B strain was assessed using the GMT ratio (GMTaTIV/GMTaQIV) and difference in SCR (SCRaTIV–SCRaQIV) at Day 22.

Superiority was declared if the upper limit of the two-sided 95% CI for the GMT ratio (aTIV/aQIV) was <1, and the upper limit of the two-sided 95% CI for the difference in SCRs (aTIV–aQIV) was <0, for both B strains.

Based on the FAS, the prespecified criteria for immunological superiority for the alternate B strain of aQIV (as measured by SCR difference and GMT ratio) relative to each aTIV vaccine were met. The results were similar in the PPS.

Table 33: Analyses of superiority of aQIV relative to aTIV for the Alternate B strain (FAS)

Table 12 Analyses of Superiority of aQIV Relative to aTIV for the Alternate B Strain (Full Analysis Set)

Strain	Comparator aTIV group	GMT Ratios aTIV/aQIV (95% CI)	Met Pre-defined Superiority Criteria for GMT ratio?	SCR (%) Difference aTIV−aQIV (95% CI [a])	Met Pre-defined Superiority Criteria for SCR Difference?
B-Yamagata	aTIV-1	0.64 (0.58, **0.70**)	Yes	-11.96 (-15.12, **-8.81**)	Yes
B-Victoria	aTIV-2	0.71 (0.64, **0.78**)	Yes	-10.82(-13.54, **-8.11**)	Yes

Abbreviations: CI=confidence interval; GMT=geometric mean titer; HI=hemagglutination inhibition; SCR=seroconversion rate.
Note 1: aQIV: MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-1: Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-2: MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain.
Note 2: GMT was the Geometric Mean of HI titers on Day 22; the GMT ratio was defined as the geometric mean of the postvaccination (Day 22) HI titer for aTIV-1 and/or aTIV-2 divided by the geometric mean of postvaccination (Day 22) HI titer for aQIV.
Note 3: GMT Adjusted Model: Log-Transformed Postvaccination HI Titer = Vaccine Group [3 vaccines] + Age Group [≥65-74, ≥75-84, and ≥85 years] + Sex [male, female] + Vaccination History [y/n] + Log-transformed Prevaccination HI Titer + Site.
Note 4: Confidence intervals for the GMT ratio were calculated based on the normality assumption of log titers.
Note 5: The SCR was defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40 or a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer.
Note 6: The SCR difference was defined as the difference between the SCR of postvaccination (Day 22) HI titer for aTIV-1 (or aTIV-2) and the SCR of postvaccination (Day 22) HI titer for aQIV ($SCR^{aTIV}-SCR_{aQIV}$).
Source: Table 14.2.1.1.2, Table 14.2.2.1.2

- Geometric mean titer and geometric mean ratio

The PPS baseline GMTs were comparable between aQIV and aTIV groups. The GMR (postvaccination/prevaccination) was also comparable in aQIV and aTIV groups for all strains: 3.36 aQIV vs. 3.29 pooled aTIV for A-H3N2 strain, and 2.99 aQIV vs. 3.40 pooled aTIV for A-H1N1 strain; 1.76 in aQIV vs. 1.68 in aTIV-1 for B-Victoria strain; and 2.03 in aQIV vs. 1.93 in aTIV-2 for B-Yamagata strain.

The highest baseline GMTs were observed against the A-H3N2 strain (73.27 aQIV, 71.83 pooled aTIV) and A-H1N1 (19.07 aQIV, 18.77 pooled aTIV), followed by B-Victoria (14.15 aQIV, 15.18 in aTIV-1), and B-Yamagata (10.41 aQIV, 10.76 aTIV-2).

Postvaccination GMT also tended to be higher for the A strains compared with the B strains. The results for the FAS were consistent with data obtained in the PPS. Baseline and postvaccination GMTs, as well as GMRs, were comparable across vaccine groups but tended to be higher for A strains compared with the B strains.

- Seroconversion rates for hemagglutination inhibition antibodies

As presented in Table below, seroconversion rates were comparable between aQIV and aTIV groups.

Seroconversion rates tended to be higher for A-H3N2 (39.33 aQIV, 39.70 pooled aTIV) and AH1N1 strains (35.21 aQIV, 38.43 pooled aTIV), compared with B-Yamagata (16.40 aQIV, 15.47 in aTIV-2), and B-Victoria (13.42 aQIV, 12.16 aTIV-1).

Table 34: Seroconversion Rates of HI antibody titers by vaccine group – As Randomised (PPS)

Strain	Measurement	aQIV vaccine (N=872)	aTIV-1 vaccine (N=436)	aTIV-2 vaccine (N=433)	aTIV-pooled (N=869)[a]
A-H1N1	n/M (%)	307/872			334/869
	95% CI of SCR[b]	35.21 (32.03, 38.48)	--	--	38.43 (35.19, 41.76)
A-H3N2	n/M (%)	343/872			345/869
	95% CI of SCR[b]	39.33 (36.08, 42.67)	--	--	39.70 (36.43, 43.04)
B-Yamagata	n/M (%)	143/872		67/433	
	95% CI of SCR[b]	16.40 (14.00, 19.03)	--	15.47 (12.20, 19.23)	--
B-Victoria	n/M (%)	117/872	53/436		
	95% CI of SCR[b]	13.42 (11.22, 15.86)	12.16 (9.24, 15.60)	--	--

Abbreviations: CI=confidence interval; HI=hemagglutination inhibition; SCR=seroconversion rate.
Note 1: aQIV: MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-1: Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-2: MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain.
Note 2: The SCR (n/M) was defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40 or a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer, where n is the number of seroconverted subjects within the vaccine group at the visit, M is the number of evaluated subjects within the vaccine group at the visit.
a aTIV-1 and aTIV-2 vaccine groups were pooled for the analysis of A-H1N1 and A-H3N2 strains. For B-Victoria TIV=aTIV-1, for B-Yamagata TIV=aTIV-2.
b Two-sided 95% CIs for SCR were the exact CIs based upon the binomial distribution.
Source: Table 14.2.4.1

- Percentage of subjects with a hemagglutinin inhibition titer ≥1:40 at day 1 and day 22

The proportions of subjects with HI titers ≥1:40 were comparable between vaccine groups for each of the 4 influenza strains at prevaccination and postvaccination.

At Day 1 (prevaccination) in the PPS, the proportion of subjects with HI titers ⩾1:40 tended to be higher in the A-H3N2 strain (70.64 aQIV and 70.66 pooled aTIV) and A-H1N1 (33.26 aQIV and 31.07 pooled aTIV) compared to B-Victoria (19.72 aQIV, 22.71 to aTIV-1) and B-Yamagata (11.12 aQIV, 11.55 aTIV-2). Similarly at postvaccination, the proportion of subjects with HI titers ⩾1:40 tended to be higher for the A strains compared with the B strains.

The results of immunogenicity analysis based on the FAS were consistent with the PPS.

- Reverse cumulative curves of hemagglutinin inhibition antibodies

The reverse cumulative distribution curves of Hemagglutinin Inhibition Antibodies by vaccine group and by strain at Day 22 for the PPS were provided within the application. There were no notable differences observed in the postvaccination HI titers across vaccine groups. Postvaccination HI titers tended to be higher for the A strains compared with the B strains. The same trend was also observed in the FAS.

Ancillary analyses

Subgroup analyses by age, gender, race, comorbidity, and vaccination history was conducted for each influenza vaccine strain for percentages of subjects with HI titer ≥1:40, GMTs, GMRs, and seroconversion rates.

- Age

The total number of subjects included in the analysis was 1,198 subjects in age group ≥65 to 74 years (602 aQIV/596 pooled aTIV); 484 subjects in age group ≥75 to 84 years (239 aQIV/245 pooled aTIV), and 59 subjects in age group ≥85 years (31 aQIV/28 pooled aTIV).

Within the aQIV group at postvaccination, there were no notable differences in the proportion of subjects with HI titer ≥1:40 against A-H1N1, A-H3N2, and B-Victoria strains in subgroup of subjects ≥65 to 74 years, ≥75 to 84 years, and ≥85 years. The proportion of subjects with HI titer ≥1:40 against B-Yamagata appeared to be reduced with age (Table 36). There were no notable differences observed in the proportion of subjects with HI ≥1:40 between aQIV and aTIV groups across subgroup of subjects of ≥65 to 74 years, ≥75 to 84 years, and ≥85 years (Table 36).

Regarding seroconversion rates, comparison of SCRs within each vaccine group across age subgroups tended to indicate a higher immune response in the ≥65 to 74 year vs. ≥75 to 84 and ≥85 year age subgroups. In general, the ≥85 years of age subgroup tended to have wider 95% CI across all influenza strains most likely due to small sample size. No substantial differences were observed for SCR between aTIV and aQIV across subgroup of subjects in the ≥65 to 74 years, ≥75 to 84 years, and ≥85 years.

In the measurements of GMT and GMR, overall across aQIV and aTIV groups, there is a trend to reduction of GMR for all influenza strains with age, with a higher GMR observed in subjects ≥65 to 74 years. No substantial differences were observed for baseline and postvaccination GMTs and GMRs between aTIV and aQIV groups across subgroup of subjects in the ≥65 to 74 years, ≥75 to 84 years, and ≥85 years.

Table 35: Percentages of subjects with HI titer ⩾1:40 and Seroconversion Rates at 22 Days postvaccination by Age Subgroup (PPS)

	Age ≥65-74 Years		Age ≥75-84 Years		Age ≥85 Years	
	aQIV n=602	aTIV-1/aTIV-2 n=596	aQIV n=239	aTIV-1/aTIV-2 n=245	aQIV n=31	aTIV-1/aTIV-2 n=28
A-H1N1						
Post-V % HI titer ≥1:40 (95% CI)	70.27 (66.44, 73.89)	72.15 (68.36, 75.71)	65.69 (59.30, 71.69)	66.12 (59.82, 72.03)	80.65 (62.53, 92.55)	67.86 (47.65, 84.12)
Seroconversion rate (%) (95% CI)	38.37 (34.47, 42.39)	41.28 (37.29, 45.35)	30.13 (24.38, 36.37)	32.24 (26.43, 38.49)	12.90 (3.63, 29.83)	32.14 (15.88, 52.35)
A-H3N2						
Post-V % HI titer ≥1:40 (95% CI)	94.85 (92.77, 96.47)	96.14 (94.27, 97.54)	91.63 (87.37, 94.81)	93.06 (89.12, 95.91)	93.55 (78.58, 99.21)	82.14 (63.11, 93.94)
Seroconversion rate (%) (95% CI)	42.69 (38.70, 46.75)	42.95 (38.94, 47.04)	33.89 (27.91, 40.27)	32.24 (26.43, 38.49)	16.13 (5.45, 33.73)	35.71 (18.64, 55.93)
B-Yamagata						
Post-V % HI titer ≥1:40 (95% CI)	34.88 (31.08, 38.84)	37.24 (31.66, 43.09)	28.87 (23.21, 35.06)	35.66 (27.42, 44.57)	22.58 (9.59, 41.10)	42.86 (17.66, 71.14)
Seroconversion rate (%) (95% CI)	18.77 (15.73, 22.12)	16.21 (12.16, 20.96)	10.88 (7.23, 15.53)	12.40 (7.26, 19.36)	12.90 (3.63, 29.83)	28.57 (8.39, 58.10)
B-Victoria						
Post-V % HI titer ≥1:40 (95% CI)	36.71 (32.85, 40.70)	35.62 (30.25, 41.27)	39.33 (33.10, 45.83)	36.21 (27.49, 45.65)	58.06 (39.08, 75.45)	71.43 (41.90, 91.61)
Seroconversion rate (%) (95% CI)	15.45 (12.65, 18.59)	14.38 (10.65, 18.82)	8.79 (5.52, 13.12)	6.03 (2.46, 12.04)	9.68 (2.04, 25.75)	14.29 (1.78, 42.81)

Abbreviations: CI=confidence interval; HI=hemagglutinin inhibition; Post-V=postvaccination; SCR=seroconversion rate.
Note 1: aQIV: MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-1: Licensed MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine; aTIV-2: MF59-adjuvanted Trivalent Subunit Inactivated Egg-derived Influenza Vaccine Containing the Alternate B Strain.
Note 2: Two-sided 95% CI for proportion of subjects with HI antibody titers ≥1:40 were based on the exact binomial.
Note 3: Two sided 95% CIs for SCR are the exact confidence intervals based upon the binomial distribution.
Note 4: aTIV-1 and aTIV-2 vaccine groups were pooled for the analysis of A-H1N1 and A-H3N2 strains. For B/Victoria TIV=aTIV-1; for B/Yamagata TIV=aTIV-2. Source: Table 14.2.2.2.1, Table 14.2.4.1.1

- Gender

Overall, a greater number of female subjects (N=983) were enrolled in the study and data analyzed compared to male subjects (N=758). At day 22 postvaccination the percentage of individuals who achieved HI titer ≥1:40 were similar between aQIV and aTIV for male and female subgroups for all strains, with no substantial differences in response by gender. This was also true for the seroconversion rates and for GMTs and GMR.

- Race

The majority of subjects enrolled in the study were white (1,593) followed by black/African American (124) subjects. Other ethnicities within the race subgroup in the study were too small for meaningful comparisons.

Overall, there are no significant differences in the responses obtained in the different races assessed in this study.

- Comorbidity/Risk Score

Comorbidity risk scores were assessed among other baseline characteristics as a validated predictor of risk of influenza complications in subjects ≥65 years of age. A score of <50 was considered low risk and a score of ≥50 was considered high risk for hospitalization due to pneumonia or influenza and death from any cause. At study entry, scores <50 and ≥50 were observed in the PPS for n=1,133 subjects and n=608 subjects, respectively.

The proportion of subjects with HI titer ≥1:40 postvaccination was similar in both aQIV and aTIV groups regardless of comorbidity risk scores.

Regarding seroconversion rates, GMT and GMR, no substantial difference was observed between aQIV and aTIV vaccines for all strains, but a trend to a lower response was observed in the high risk group for both vaccines.

- Vaccination history

A significantly greater number of subjects reported having a vaccination history (1,512 subjects) vs. 229 subjects reporting no vaccination history.

Baseline and postvaccination proportion of subjects with HI titer ≥1:40 tended to be higher for A strains compared with the B strains in the subgroup of subjects with and without vaccination history. Subjects in both aQIV and aTIV vaccine groups had similar immune responses regardless of vaccination history.

Overall, subjects without vaccination history within the last 5 years tended to have a higher GMR and SCR than subjects with a history of vaccination, however, the postvaccination HI titers are comparable in these subgroups for A-H1N1 and A-H3N2 strains.

2.5.4.2. V70_27

V70_27 A Phase 3, Randomized, Controlled, Observer-Blind, Multicentre Study to Evaluate the Safety and Immunogenicity and the Consistency of Three Consecutive Lots of a MF59C.1 Adjuvanted Trivalent Subunit Influenza Vaccine in Elderly Subjects Aged 65 Years and Older.

Methods

Study Participants

Males and females of age ≥65 years on the day of vaccination, willing and able to participate in the study were included.

Inclusion criteria

Males and females of age ≥65 years on the day of vaccination, willing and able to participate in the study.

Exclusion criteria

Any suspected impairment of the immune system are excluded, besides the regular exclusion criteria, and history of Guillain-Barré syndrome.

Treatments

Subjects were to receive either 1 of the 3 lots of aTIV (lots 1, 2, or 3) or TIV vaccine. aTIV and TIV contained two A-strains (A/California/7/2009 (H1N1)-like strain and A/Perth/16/2009 (H3N2)-like strain) and one B-strain (B/Brisbane/60/2008-like strain).

Objectives

Primary objective

To evaluate the superiority of aTIV compared to TIV with regards to at least 2 homologous strains and to demonstrate the noninferiority of aTIV compared to TIV with regards to all homologous strains in adults ≥65 years of age as measured by GMT ratios and seroconversion rate differences at day 22.

In addition there was a co-primary objective with regards to lot to lot consistency for three consecutive production lots of aTIV as measured by HI GMTs at day 22 for each virus strain. As this has limited relevance to the current application, this objective is not further discussed in this overview.

Main secondary objectives

To evaluate the superiority of aTIV compared to TIV with regards to at least 2 heterologous strains and to demonstrate the noninferiority of aTIV compared to TIV with regards to all heterologous strains in adults ≥65 years and in high-risk subjects with predefined comorbidities as measured by GMT ratios and seroconversion rate differences at day 22.

To assess the difference between aTIV and TIV with regards to homologous and heterologous strains in subjects included in the antibody persistence group as measured by GMT ratios and seroconversion rate differences at day 181 and day 366.

Outcomes/endpoints

The immunogenicity endpoints based on the HI titre were comparisons between pairs of aTIV lots and comparisons of the aTIV with the TIV vaccines for the variables shown below. Co-primary endpoints were evaluated at day 1 and day 22, and secondary endpoints were evaluated at day 1, day 22, day 181, and day 366.

- GMT, GMR of day X/day 1 HI titres (where day X is day 22, day 181, or day 366);
- Percentage of subjects achieving seroconversion;
- Percentage of subjects achieving HI titre ≥40.

Seroconversion was defined as for subjects with negative pre-vaccination HI serum titre (<10) a postvaccination titre ≥40 or, for subjects with a non negative prevaccination titre (≥10), at least a 4-fold increase in HI serum titre from baseline

Randomisation

Subjects were randomised to receive either 1 of the 3 lots of aTIV (investigational vaccine; lots 1, 2, or 3) or TIV vaccine (active control) with ratio 1:1:1:3 and were stratified into 2 age cohorts, 65 to 75 years and >75 years. According to the protocol the age groups should have been 65 to 74 years and ≥ 75 years, which is different from the performed randomisation.

Blinding (masking)

The administration of the vaccines was performed by an unblinded designated person. All other personnel was planned to be blind.

Statistical methods

Analysis Sets:

Full Analysis Set (FAS), Immunogenicity Day 22: All randomised subjects who received a study vaccination and provided evaluable serum samples both at day 1 and at day 22.

Per Protocol Set (PPS), Immunogenicity Day 22: All subjects in the FAS who received the correct vaccine and had no major protocol deviation prior to unblinding.

FAS, Antibody Persistence Testing: All randomised subjects at US sites who (i) received a study vaccination and (ii) provided evaluable blood samples at day 1, day 22, day 181, and day 366. This subset of 700 subjects was randomly selected from among all subjects at United States sites, thus the antibody persistence subset was not representative of the entire study population.

Modified Full Analysis Set (mFAS), Effectiveness: All subjects included in the Effectiveness FAS, but for those subjects who received a non-study influenza vaccination during the follow-up phase, any ILI/health care utilization/exacerbation of pre-existing chronic diseases/deaths occurring after the non-study vaccination were not included in the analysis.

Primary Immunogenicity Analysis

Non-Inferiority

All non-inferiority analyses were performed on the PPS Immunogenicity Day 22.

GMT at Day 22: For each of the 3 strains, log-transformed GMT values were analysed by using ANCOVA model with factors vaccine group, country, age and with covariate log-transformed pre-vaccination antibody titre. Point estimates and 2-sided 95% CIs for ratios of GMTs (aTIV/TIV) were based on these analyses.

SCR at Day 22: For each of the 3 strains, seroconversion rates (binary data) were analysed by using log-linear models with factors vaccine group, country, and age. Vaccination group differences (aTIV – TIV) along with 95% CIs were based on this model.

To assess non inferiority of a TIV vs. TIV, the lower limit of the 95% CI for GMT ratio needs to be >0.67 and the lower limit of the 95% CI for the SCR difference needs to be >-10% for all 3 strains.

Superiority

All superiority analyses were performed on the FAS Immunogenicity Day 22

The family of six superiority hypotheses was tested applying a multiple test procedure that keeps the familywise error rate at 1-sided α=2.5%. The Holm–Bonferroni method was applied.

GMT and SCR at Day 22 were analysed using the same models as was used for the non-inferiority analyses. Point estimates and multiplicity unadjusted 2-sided 95% confidence intervals for ratios of GMTs and difference of SCR were based on these models.

To adjust for multiplicity, adjusted p-values were calculated using the method described by Dmitrienko et al (2010). Simultaneous confidence intervals for step-wise procedures with differently scaled endpoints (binary and normal distributed in the present study) are not available. Therefore all confidence intervals provided will not take multiplicity into consideration.

To assess superiority of aTIV vs. TIV, the lower limit of the 95% CI for GMT ratio needs to be >1.5 and the lower limit of the 95% CI for the SCR difference needs to be >10% for at least 2 of the 3 strains.

Interim Analysis: The final results were based on data from the interim analysis.

Multiplicity

The **confirmatory testing strategy** was planned in a sequential order.

First, the lot-to-lot consistency was to be tested. Then if, and only if, consistency is confirmed (i.e., rejection of null hypothesis), the non-inferiority test for the 6 primary endpoints was to be conducted. Then if, and only if, non-inferiority was confirmed, the superiority test for the 6 primary endpoints was conducted. The study was powered to show lot-to-lot consistency and the co-primary objective.

The Holm-Bonferroni method was used for the multiplicity introduced by the superiority objective.

Handling Missing data: The applicant considered missing immunogenicity values as MCAR's.

Sensitivity analyses: All primary immunogenicity analyses were performed for both the FAS Immunogenicity Day 22 population and for the PPS Immunogenicity Day 22 population.

Statistical Analysis Plan Amendments

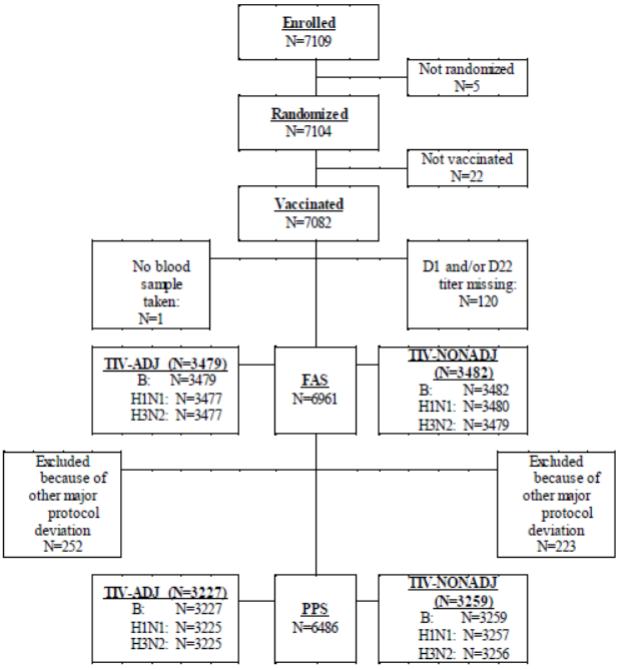
The SAP was amended 2 times. After unblinding of the data several additional analyses were performed and were specified in 3 addendums. One was an additional superiority testing with other superiority margins 1.0 and 0% besides superiority margins 1.5 and 10% as was chosen for the primary immunogenicity objective.

Results

Participant flow

Overall 7,109 subjects were enrolled into the study, 7,082 were randomized and vaccinated, and 6,717 subjects (94%) completed the study.

Figure 3: Participant flow



Recruitment

Study V70_27 was conducted 38 centres distributed along Colombia (4), Panama (2), The Philippines (11) and United States (21). The study is conducted in the 2010/2011 influenza season.

Conduct of study

There were 4 protocol amendments, and 9% of the subjects had at least one major protocol deviation.

Baseline data

The baseline and demographic characteristics of subjects in the day 22 FAS were closely matched between the two vaccine groups. The mean age of all subjects was 72 years (range: 65 to 97 years), with 28% of subjects over 75 years of age (28% and 27% in the aTIV and TIV groups, respectively). A higher proportion of females than males was enrolled (65% overall) with similar proportions in the two vaccine groups. The main racial and ethnic groups represented were Asian (53%), Caucasian (28%), and Hispanic (18%) in each of the vaccine groups. The demographic and baseline characteristics of the FAS are provided in the table below. About 36% (n=2,573) of all randomized subjects in the day 22 FAS were high-risk; most of these subjects were included in the day 22 PPS (34% of randomized subjects; n=2,385).

Table 36: Demographic and baseline characteristics FAS (V70_27)

	TIV-ADJ N=3479	TIV-NONADJ N=3482	Total N=6961
Age (Mean ± SD; years)	71.9±5.3	71.8±5.3	71.9±5.3
Gender:			
Male	1252 (36%)	1178 (34%)	2430 (35%)
Female	2227 (64%)	2304 (66%)	4531 (65%)
Age Cohorts:			
65-75 years	2504 (72%)	2531 (73%)	5035 (72%)
>75 years	975 (28%)	951 (27%)	1926 (28%)
Country:			
Colombia	503 (14%)	495 (14%)	998 (14%)
Panama	108 (3%)	102 (3%)	210 (3%)
Philippines	1832 (53%)	1830 (53%)	3662 (53%)
United States	1036 (30%)	1055 (30%)	2091 (30%)
Ethnic Origin:			
Asian	1837 (53%)	1840 (53%)	3677 (53%)
Black	44 (1%)	39 (1%)	83 (1%)
Caucasian	969 (28%)	971 (28%)	1940 (28%)
Hispanic	616 (18%)	613 (18%)	1229 (18%)
Other	11 (<1%)	16 (<1%)	27 (<1%)
Native American/Alaskan	1 (<1%)	3 (<1%)	4 (<1%)
Pacific/Hawaii	1 (<1%)	0	1 (<1%)
Weight (kg):	63.36±19.50	63.39±19.35	63.37±19.42
Height (cm):	156.89±11.58	156.74±11.48	156.81±11.53
Body Mass Index (kg/m^2):	25.36±5.67	25.43±5.62	25.39±5.64
Previous Pneumococcal Vaccination:			
Yes	739 (21%)	717 (21%)	1456 (21%)
No	2627 (76%)	2664 (77%)	5291 (76%)
Not done / unknown	113 (3%)	101 (3%)	214 (3%)
Previous H1N1 Vaccination:			
Yes	79 (2%)	74 (2%)	153 (2%)
No	3389 (97%)	3396 (98%)	6785 (97%)
Not done / unknown	11 (<1%)	12 (<1%)	23 (<1%)
H1N1 Disease:			
Yes	1 (<1%)	2 (<1%)	3 (<1%)
No	3476 (100%)	3474 (100%)	6950 (100%)
Not done / unknown	2 (<1%)	6 (<1%)	8 (<1%)

Numbers analysed

As per protocol, 1,768 subjects (25% of randomized subjects across vaccine groups) were randomly selected for inclusion in the day 22 FAS for immunogenicity analysis using heterologous strains. The majority of these subjects were retained for the day 22 PPS for heterologous testing (1,649 subjects; 23% of all randomized subjects). Baseline characteristics of the FAS immunogenicity are in line with the overall enrolled population.

Outcomes

Superiority of aTIV versus TIV for homologous strains.

For the A/H1N1 and B strains, the vaccine group GMT ratios (aTIV:TIV) were 1.37 (lower bound of 95% CI: 1.29) and 1.14 (lower bound of 95% CI: 1.08), respectively; for the A/H3N2 strain, the ratio was 1.6 (lower bound of 95% CI: 1.51). Only the LL of the 95% CI for the day 22 GMT ratio for the A/H3N2 strain was >1.5, meeting the predefined criterion for superiority. However, after adjusting for multiple comparisons the p-value was 0.055. Therefore superiority could not be claimed according to the predefined criteria.

The adjusted day 22 GMTs against each of the 3 homologous strains in the aTIV group were higher than those of the TIV group.

Table 37: Geometric mean HI titres (95% CI) and vaccine group ratios against homologous strains day 22 FAS (V70_27)

		TIV-ADJ	TIV-NONADJ	TIV-ADJ: TIV-NONADJ	Unadjusted p-value		Multiplicity-adjusted p-value	
		N=3477	N=3480		Difference	Superiority	Difference[a]	Superiority[b]
A/California/7/2009-like (H1N1)	Day 1 (95% CI)	7.8 (7.37-8.24)	7.76 (7.33-8.2)	1.01 (0.95-1.06)				
	Day 22[c] (95% CI)	98 (92-104)	71 (67-76)	1.37 (1.29-1.46)	<0.0001	0.998	<0.001	1.000
	Day 22: Day 1 (95% CI)	13 (13-14)	9.77 (9.14-10)	1.37 (1.28-1.47)				
		N=3477	N=3479					
A/Perth/16/2009-like (H3N2)	Day 1 (95% CI)	27 (25-29)	26 (24-28)	1.03 (0.95-1.11)				
	Day 22[c] (95% CI)	267 (253-282)	167 (158-176)	**1.6 (1.51-1.68)**	<0.0001	0.011	<0.001	0.055
	Day 22: Day 1 (95% CI)	10 (9.49-11)	6.54 (6.06-7.06)	1.57 (1.45-1.69)				
		N=3479	N=3482					
B/Brisbane/60/2008-like	Day 1 (95% CI)	6.2 (5.94-6.46)	6.14 (5.89-6.4)	1.01 (0.97-1.05)				
	Day 22[c] (95% CI)	27 (26-29)	24 (23-25)	1.14 (1.08-1.2)	<0.0001	1.000	<0.001	1.000
	Day 22: Day 1 (95% CI)	4.85 (4.59-5.13)	4.28 (4.04-4.52)	1.14 (1.07-1.2)				

Source: Table 14.2.1.1.7; Appendix 16.1.9.1.6-1, Appendix 16.1.9.1.6-3.
Abbreviations: CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer; HI = hemagglutination inhibition.
Bold: TIV-ADJ superior to TIV-NONADJ (lower bound of 95% CI of vaccine group ratio ≥1.5; CI values are not adjusted for multiplicity).
[a] Difference: 2-sided p-value used to test whether TIV-ADJ/TIV-NONADJ ratio is different from 1.0.
[b] Superiority: 1-sided p-value used to test whether TIV-ADJ/TIV-NONADJ ratio is ≥1.5.
[c] Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ:TIV-NONADJ) are adjusted for day 1 titer, country, and age cohort.

Superiority of aTIV to TIV defined as Δ SCR >10% was achieved for A/H3N2. The lower bound of the 95% CI for the aTIV minus TIV difference in day 22 seroconversion rates for the A/H3N2 strain was >10% (Δ=13.8%, 95% CI: 11.7, 16), with an unadjusted p-value for superiority of 0.0004, after adjusting for multiple comparisons the p-value was 0.002.

The adjusted difference in percentage of subjects who seroconverted by day 22 was higher in the aTIV group than in the TIV group for each of the homologous strains tested. For the A/H1N1 and B strains, the differences were 9.6% (95% CI: 7.4, 11.8) and 3% (95% CI: 1, 7), respectively.

Table 38: Percentage (95% CI) of subjects with seroconversion and vaccine group differences against homologous strains day 22 FAS.(V70_27)

	TIV-ADJ	TIV-NONADJ	TIV-ADJ – TIV-NONADJ[b]	Unadjusted p-value		Multiplicity-adjusted p-value	
	N=3477	N=3480		Difference	Superiority	Difference[c]	Superiority[d]
A/California/7/2009-like (H1N1)	68% (67%-70%)	59% (57%-60%)	9.6% (7.4%-11.8%)	<0.0001	0.663	<0.001	1.000
	N=3477	N=3479					
A/Perth/16/2009-like (H3N2)	72% (71%-74%)	58% (56%-60%)	**13.8% (11.7%-16%)**	<0.0001	0.0004	<0.001	0.002
	N=3479	N=3482					
B/Brisbane/60/2008-like	33% (31%-34%)	30% (28%-31%)	3% (1%-5%)	0.0021	1.000	0.002	1.000

Source: Table 14.2.1.1.8; Appendix 16.1.9.1.6-1, Appendix 16.1.9.1.6-3.
Abbreviations: CI = confidence interval; FAS = full analysis set; HI = hemagglutination inhibition.
Bold: TIV-ADJ superior to TIV-NONADJ (lower bound of 95% CI of vaccine group difference ≥10%).
[a] Seroconversion defined as prevaccination HI titer <10 and postvaccination HI titer ≥40 or an increase in HI titer of at least 4-fold from a prevaccination HI titer of ≥10.
[b] Day 22 vaccine group differences are adjusted for country and age cohort and therefore may not equal the difference between the two columns to the left. Vaccine group percentages are unadjusted.
[c] Difference: multiplicity-adjusted 2-sided p-value used to test whether the adjusted TIV-ADJ minus TIV-NONADJ difference is different from 0%.
[d] Superiority: multiplicity-adjusted 1-sided p-value used to test whether the adjusted TIV-ADJ minus TIV-NONADJ difference exceeds 10%.

Superiority of aTIV compared with TIV for **heterologous** strains

The day 22 GMTr was 1.49 (95% CI: 1.29, 1.72), 1.38 (95% CI:1.24, 1.52) and 1.09 (95%CI: 0.99, 1.21) for the three strains respectively. This means that aTIV showed higher GMT values compared with TIV. The results for the GMRs were similar.

The difference in SCR (aTIV-TIV) was 12.8% (95% CI: 8.4, 17.2) for A/H1N1, 12.5% (95%CI: 0.1, 17) for A/H3N2 and 4.2% (95%CI: 0, 8.4) for the B-strain against heterologous test strains. The adjusted differences in percentage of subjects that seroconverted to both of the A/H3N2 strains, but not the B strain, by day 22 were higher in the aTIV group compared with the TIV.

Comparison of aTIV and TIV in **antibody persistence** subset

Antibody persistence was assessed by GMT and seroconversion rates in serum samples from day 181 (6 months) and day 366 (1 year) postvaccination.

Table 39: Geometric mean HI titres (95% CI) and vaccine group ratios against homologous strains FAS (persistence) (V70_27)

		TIV-ADJ	TIV-NONADJ	TIV-ADJ : TIV-NONADJ
A/California/7/2009-like (H1N1)		N=189	N=191	
	Day 1	17 (14-20)	19 (16-23)	0.9 (0.69-1.18)
	Day 22	85 (70-102)	72 (60-87)	1.17 (0.9-1.51)
	Day 22: Day 1	4.98 (4.17-5.95)	3.85 (3.22-4.59)	**1.3 (1.01-1.66)**
	Day 181	35 (30-42)	34 (29-40)	1.05 (0.82-1.33)
	Day 181: Day 1	2.09 (1.77-2.45)	1.8 (1.53-2.12)	1.16 (0.92-1.46)
	Day 366	25 (21-30)	26 (22-31)	0.94 (0.73-1.22)
	Day 366: Day 1	1.45 (1.24-1.7)	1.39 (1.19-1.63)	1.04 (0.84-1.3)
A/Perth/16/2009-like (H3N2)		N=189	N=191	
	Day 1	22 (18-26)	22 (18-26)	1 (0.77-1.29)
	Day 22	131 (110-156)	92 (77-109)	**1.42 (1.11-1.82)**
	Day 22: Day 1	6.08 (5.05-7.32)	4.27 (3.55-5.13)	**1.42 (1.1-1.85)**
	Day 181	62 (52-73)	46 (39-54)	**1.35 (1.06-1.71)**
	Day 181: Day 1	2.87 (2.44-3.37)	2.12 (1.81-2.49)	**1.35 (1.08-1.7)**
	Day 366	35 (29-42)	27 (23-32)	**1.3 (1.01-1.67)**
	Day 366: Day 1	1.63 (1.4-1.89)	1.25 (1.08-1.45)	**1.3 (1.05-1.61)**
B/Brisbane/60/2008-like		N=189	N=191	
	Day 1	12 (9.91-14)	12 (10-14)	0.97 (0.78-1.2)
	Day 22	25 (22-29)	21 (18-24)	1.21 (0.98-1.49)
	Day 22: Day 1	2.2 (1.97-2.46)	1.76 (1.58-1.97)	**1.25 (1.07-1.46)**
	Day 181	12 (11-15)	11 (9.51-13)	1.12 (0.9-1.39)
	Day 181: Day 1	1.07 (0.98-1.17)	0.93 (0.85-1.02)	**1.16 (1.02-1.31)**
	Day 366	10 (8.84-12)	9.96 (8.58-12)	1.03 (0.83-1.27)
	Day 366: Day 1	0.89 (0.81-0.98)	0.83 (0.76-0.91)	1.07 (0.93-1.22)

Source: Table 14.2.1.7.1.
Abbreviations: CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer.
Bold: Vaccine group GMT ratio significantly higher in the TIV-ADJ group than in the TIV-NONADJ group (lower bound of 95% CI >1).

By day 181, GMTs against **homologous strains** in both vaccine groups had declined compared with day 22. However, as shown, GMTs against the homologous A/H3N2 strain at day 181 and day 366 were higher in the aTIV group than in the TIV group (day 181: 1.35 [95% CI: 1.06-1.71] and day 366: 1.3 [95% CI: 1.01- 1.67]). Similar results were seen for seroconversion rates with a significantly greater percentage of subjects in the aTIV group than in the TIV group with seroconversion against the homologous A/H3N2 strain (difference of 11.9%) at day 181. By day 366, the difference had decreased to 3.8% (NS).

By day 181, antibody levels against **heterologous strains** had declined in both vaccine group subsets with no significant difference in GMTs at day 181 or day 366 against the heterologous strains tested. Similarly, no difference at day 181 and day 366 between the vaccine groups was found considering the SCR.

Ancillary analyses

Age

The applicant presented the immune response in the following age strata: ≥65 – 75 years and >75 years. At day 22, the adjusted GMT ratios indicated a higher response in the aTIV group than in the TIV group against all 3 homologous strains in both age cohorts, and the size of the benefit was sustained in the older age group as the GMT ratios were similar. The response was higher in persons age 65- 75 years for the A-strains (i.e. the GMR D22/D1 was higher in ≥65-75 vs >75 years) but not for the B

strain, where GMRs were similar in both age groups (Table 41). Results were similar considering the endpoint seroconversion (Table 42).

Table 40: Analysis by age cohort of GMTs and vaccine group GMT ratios (95% CIs) against homologous strains day 22 FAS (V70_27)

		65 to 75 Years			>75 Years		
		TIV-ADJ	TIV-NONADJ	TIV-ADJ: TIV-NONADJ	TIV-ADJ	TIV-NONADJ	TIV-ADJ: TIV-NONADJ
A/California/7/2009-like (H1N1)		N=2502	N=2529		N=975	N=951	
	Day 1	6.43 (6.12-6.76)	6.42 (6.11-6.74)	1 (0.94-1.07)	7.9 (7.26-8.59)	7.92 (7.27-8.63)	1 (0.88-1.12)
	Day 22[a]	95 (90-100)	70 (66-73)	**1.37 (1.27-1.47)**	95 (88-104)	68 (62-74)	**1.41 (1.25-1.59)**
	Day 22 to Day 1	15 (14-16)	11 (10-11)	1.37 (1.26-1.49)	12 (11-13)	8.54 (7.74-9.42)	1.41 (1.23-1.62)
A/Perth/16/2009-like (H3N2)		N=2502	N=2528		N=975	N=951	
	Day 1	24 (23-26)	23 (22-25)	1.03 (0.95-1.13)	26 (24-29)	26 (23-28)	1.02 (0.89-1.17)
	Day 22[a]	304 (290-319)	189 (180-198)	**1.61 (1.5-1.72)**	272 (251-293)	171 (158-185)	**1.59 (1.43-1.78)**
	Day 22 to Day 1	13 (12-14)	8.1 (7.58-8.65)	1.57 (1.43-1.73)	10 (9.39-11)	6.61 (5.96-7.32)	1.57 (1.36-1.82)
B/Brisbane/60/2008-like		N=2504	N=2531		N=975	N=951	
	Day 1	4.79 (4.62-4.97)	4.71 (4.53-4.88)	1.02 (0.97-1.07)	6.92 (6.46-7.41)	7.13 (6.65-7.64)	0.97 (0.88-1.07)
	Day 22[a]	22 (21-23)	19 (18-20)	**1.14 (1.07-1.22)**	32 (30-35)	28 (26-30)	**1.15 (1.04-1.28)**
	Day 22/1	4.63 (4.41-4.86)	4.09 (3.9-4.29)	1.13 (1.06-1.21)	4.66 (4.28-5.06)	3.98 (3.65-4.33)	1.17 (1.04-1.32)

Source: Table 14.2.1.5.1.
Abbreviations: CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer.
Bold: Day 22 Vaccine group GMT ratio significant (lower bound of 95% CI >1).
[a]Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ:TIV-NONADJ) are adjusted for baseline titer.

Table 41: Percentage (95% CI) of subjects by age cohort with seroconversion against homologous strains day 22 FAS (V70_27)

		65 to 75 Years			>75 Years		
		TIV-ADJ	TIV-NONADJ	TIV-ADJ – TIV-NONADJ	TIV-ADJ	TIV-NONADJ	TIV-ADJ – TIV-NONADJ
A/California/7/2009-like (H1N1)		N=2502	N=2529		N=975	N=951	
	Day 22	70% (68%-72%)	60% (58%-62%)	**10.1% (7.5% - 12.7%)**	65% (62%-68%)	56% (53%-59%)	**9.1% (4.7% - 13.4%)**
A/Perth/16/2009-like (H3N2)		N=2502	N=2528		N=975	N=951	
	Day 22	74% (72%-75%)	59% (58%-61%)	**14.1% (11.5% - 16.7%)**	69% (65%-71%)	54% (51%-57%)	**14.4% (10.1% - 18.7%)**
B/Brisbane/60/2008-like		N=2504	N=2531		N=975	N=951	
	Day 22	32% (30%-33%)	29% (27%-30%)	2.9% (0%-5.4%)	36% (33%-39%)	32% (29%-35%)	4.1% (0%-8.4%)

Source: Table 14.2.1.5.2.
Abbreviations: CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer.
Bold: Day 22 Vaccine group differences significant with a lower bound of 95% CI of >0%.
[a]Seroconversion defined as prevaccination HI titer <10 and postvaccination HI titer ≥40 or at least a 4-fold increase in HI from prevaccination HI titer ≥10.

Sex

There were more women than men in each vaccine group (in both the FAS and the PPS: aTIV 64% female and TIV 66%. For females there was a slightly higher response for the two A-strains after aTIV as well as after TIV (GMT and seroconversion) compared to males, but not for the B strains.

Comorbidities

In study V70_27 high-risk subjects had 1 or more of the following predefined comorbidities, with no substantive differences between vaccine groups: congestive heart failure (6%), chronic obstructive pulmonary disease (COPD; 13% to 14%), asthma (12%), hepatic diseases (<1% to 1%), renal insufficiency (4% to 5%), and the most commonly reported neurological/neuromuscular or metabolic conditions including diabetes mellitus (82% to 83%).

2.5.4.3. V118_18

Study V118_18, a Phase III, Randomized, Observer-Blind, Controlled, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared to Non-influenza Vaccine Comparator in Adults ≥ 65 Years of Age.

Methods

The goal of this randomized, observer-blind, controlled study was to demonstrate that Fluad Tetra prevents influenza in elderly adults. Direct comparison with a non-influenza comparator vaccine (Boostrix) licensed for use in this age group, enabled an estimation of the absolute efficacy of aQIV in preventing influenza in elderly adults while simultaneously providing benefit to subjects randomized to not receive influenza vaccine. The study was conducted during the NH 2016/17 and SH 2017 influenza seasons.

The study enrolled male and female adults ≥ 65 years old who were healthy or had co-morbidities. Subjects were randomized in a 1:1 ratio and were subsequently followed up for 12 months. Each subject had two stages of study participation: Treatment Period (Day 1 to Day 22) and Follow-up Period (Day 23 to Day 366).

Whenever nasopharyngeal swabs were collected, they were processed for viral culture and RT-PCR confirmation. The viral culture was used for viral expansion to enable antigenic characterization of the influenza virus (e.g. antigenic match).

The secondary immunogenicity objective was assessed by HI assay conducted on serum samples collected before vaccination on Day 1 and on Day 22 by titrating antibodies against homologous influenza strains.

A protocol specified unblinded interim analysis was conducted by the Data Monitoring Committee on 03 Aug 2017 for evaluation of the primary efficacy objective (VE against any influenza) using 167 RT-PCR confirmed influenza cases exclusively from the NH 2016/17 season.

Study participants

Planned: In order to obtain 238 PCR-confirmed influenza cases and assuming a drop-out rate of 10%, approximately 10692 subjects ≥65 years, 5,346 per vaccine group were to be randomized to receive either aQIV or non-influenza comparator (Boostrix) in a 1:1 allocation ratio.

Treatments

The products to be used in the clinical trial are:

1. Investigational Vaccine: aQIV a 0.5 mL dose of aQIV (quadrivalent MF59C.1 adjuvanted influenza vaccine) contained 60 µg of hemagglutinin (HA): 15 µg of HA of each of the two influenza type

A strains and each of the two influenza type B strains recommended by WHO for the 2016-2017 NH and 2017 SH influenza seasons for quadrivalent.

2. Boostrix is a combined Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine

Objectives

The primary and secondary efficacy objectives were measured in all subjects in relation to cases of influenza occurring from ≥21 through ≤180 days after vaccination or until the end of influenza season, whichever was longer. In all cases, efficacy was determined based on influenza cases caused by A (H1N1 and H3N2) and either B lineage.

Primary Efficacy Objective:

1. To demonstrate absolute vaccine efficacy (VE) of aQIV versus non-influenza comparator (Boostrix) when administered as a single dose to prevent first occurrence RT-PCR confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine, in subjects ≥ 65 years of age.

Key Secondary Efficacy Objective:

1. To demonstrate absolute VE of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to strains antigenically matched to the strains selected for the seasonal vaccine.

Secondary Efficacy Objectives:

2. To evaluate absolute VE of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine.

3. To evaluate absolute VE of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to strains antigenically unmatched to the strains selected for the seasonal influenza vaccine.

4. To evaluate the absolute efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence RT-PCR confirmed influenza due to any strain of influenza regardless of antigenic match from 7 days to 180 days after vaccination or at the end of influenza season, whichever was longer (early efficacy).

Secondary Immunogenicity Objectives:

5. To evaluate the immunogenicity of aQIV measured by Hemagglutination inhibition (HI) titer 21 days after vaccination, against influenza strains homologous to the seasonal vaccine.

Exploratory Immunogenicity Objective:

6. To characterize the immunogenicity of aQIV using other immunological assays (such as microneutralization [MN] assay).

7. To explore potential immune correlates of protection based on HI and/or other immunological assays (such as MN assay).

Outcomes/endpoints

The primary and the secondary efficacy objectives 1-4 were analyzed using two ILI definitions for influenza. Below are found the primary efficacy endpoint.

Primary Endpoints

- Primary Efficacy Endpoint

The primary Efficacy Endpoint was the time to first occurrence of RT-PCR confirmed influenza from 21 through 180 days after vaccination or end of the influenza season, whichever was longer. The end of the influenza season was defined as the end of June for NH influenza season and the end of December for SH influenza season. For tropical countries, the season was defined using the strains in the vaccine formulation (i.e. strains as recommended for the NH or the SH influenza season) and the timing of vaccination.

The primary protocol-definition of ILI was used to determine success for the primary and secondary efficacy endpoints. All primary and secondary efficacy objectives were also analysed using the modified CDC ILI definition.

Randomisation

aQIV or non-influenza comparator (Boostrix) in a 1:1 allocation ratio.

Blinding (masking)

The administration of the vaccines was performed by an unblinded designated person.

Statistical methods

The Statistical Analysis Plan version 2.0 provides the description of the analysis for the active study period and safety follow-up through to the final evaluation (12 months following last study vaccination dose), sample size, and power considerations.

Analysis Sets:

- Full Analysis Set (FAS) Efficacy: Subjects in the All Enrolled Set who were randomized and received a study treatment, were under observation for at least 21 days post-vaccination and provided efficacy data.
- Full Analysis Set Immunogenicity: Randomly selected sample of 1702 subjects, including subjects from both treatment arms (1362 aQIV; 340 Boostrix), in the All Enrolled Set who were randomized, received a study treatment, and provided immunogenicity data at Days 1 and 22.
- Per Protocol Set (PPS) for Efficacy/Immunogenicity analysis includes subjects who:
    - Correctly received the vaccine (i.e., received the vaccine to which the subjects were randomized to receive).
    - Had no Clinical Study Report (CSR)-reportable protocol deviation leading to exclusion as defined prior to unblinding.
    - Were not excluded due to other reasons defined prior to unblinding

Analysis of Efficacy Objectives

Primary and key secondary VE data were analyzed using the FAS Efficacy and PPS Efficacy sets. All non-key secondary VE objectives were analyzed using FAS Efficacy and repeated on PPS.

Primary and Secondary Efficacy Objectives:

The primary measure of absolute efficacy was tested in elderly subjects ≥ 65 years of age according to the following null (H0) and alternative (H1) hypotheses: H0: 1- HR = VE ≤ 0.4 versus H1: VE > 0.4 where HR is the hazard ratio of the incidence of protocol-defined ILI in aQIV versus a non-influenza comparator estimated by the proportional hazards model and VE is vaccine efficacy. One interim analysis was performed. To control the overall type 1 error alpha ≤ 0.05, the CIs for the final analysis of primary efficacy objective were adjusted accordingly. The primary efficacy and key secondary efficacy objectives were considered achieved if the lower limit (LL) of the adjusted two-sided 95% CI of absolute VE exceeded 40%.

Post-hoc Analysis: VE using the standard CDC ILI Definition and the WHO ILI definition: VE estimates were calculated using similar analyses as the primary and secondary efficacy objectives.

Immunogenicity

Immunogenicity data were analyzed using FAS Immunogenicity and repeated using PPS Immunogenicity if more than 5% of subjects were excluded from FAS Immunogenicity. All statistical analyses for HI titers were performed on the logarithmically (base 10) transformed values. Individual HI titers below detection limit (< 10) were set to half of that limit (5). Crude estimates for GMTs, GMRs and pertaining two-sided 95% CIs were calculated assuming lognormal distribution of the titers and were completed by providing minimum, maximum and median titers for each vaccine group.

Binary data (i.e., percentages of subjects with seroconversion and with titer ≥ 1:40) were summarized for each group using unadjusted estimates and was reported together with two-sided 95% CIs.

Immunogenicity endpoints at Day 22 were assessed according to the criteria for sufficient immune response described in Center for Biologics Evaluation and Research (CBER) Guidance 'Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines' (2007) states the following:

- The lower limit (LL) of the two-sided 95% confidence intervals (CI) for the percent of subjects achieving seroconversion for HI antibody should have met or exceeded 30%.
- The LL of the two-sided 95% CI for the percent of subjects who achieved an HI antibody titer ≥ 1:40 should have met or exceeded 60%.

Results

The following changes were made to the planned analysis:

• Since the study failed to reach primary objectives, the key secondary objectives were tested at alpha=0.05.

The exploratory immunogenicity objectives (immunogenicity of aQIV using other immunological assays and potential immune correlates of protection) were not evaluated as part of the current analyses.

No significant amendments were performed on the Statistical Analysis Plan.

Changes Following Study Unblinding and Post-hoc Analyses: Additional post-hoc analyses to demonstrate VE using WHO and standard CDC definition for ILI were performed.

Participant flow

Overall, 6,790 subjects were enrolled in this study. Of these, 6,761 (99.6%) subjects were exposed to study treatments with a similar number of subjects exposed to aQIV and Boostrix (3,379 received aQIV and 3,382 received Boostrix). Most enrolled subjects (6,536 [96.3%]) completed the study. The proportion of subjects that discontinued the study was low (254 subjects [3.7%]).

Recruitment

This study was conducted between 30 September 2016 and 23 July 2018 at 89 sites in 12 countries: 11 sites in Bulgaria, 7 sites in Colombia, 5 sites in Czech Republic, 6 sites in Estonia, 4 sites in Latvia, 7 sites in Lithuania, 8 sites in Malaysia, 6 sites in the Philippines, 15 sites in Poland, 8 sites in Romania, 4 sites in Thailand, and 8 sites in Turkey.

Conduct of the study

Interim Analysis

According to the prespecified rule described above, one unblinded interim analysis was conducted by the DMC on 03 Aug 2017 for evaluation of the primary efficacy objective (VE against any RT-PCR confirmed influenza) using 167 RT-PCR confirmed influenza cases exclusively from the NH 2016/17 season. The DMC informed Seqirus that "based solely on the charter's statistical rule for stopping, the study reached the pre-specified stopping p-value for futility for the primary efficacy objective, however, Seqirus may choose to continue the study to completion for clinical or epidemiological reasons given that there is no safety reason to stop the study." Seqirus opted to continue the study while remaining completely blinded. As a consequence of the interim analysis, the CIs of the final primary efficacy analysis were updated from 95% to 97.45% to control the overall type I error under 5%.

Baseline data

Overall, the demographic and baseline characteristics of subjects enrolled in this study were well balanced between the two vaccine groups with similar age, sex, ethnicity, race, and BMI.

Twenty-seven percent (27.2%) of subjects had a high comorbidity score (≥ 50). Most of the subjects (6130 [90.3%]) were non-smokers. Approximately 60% of the subjects were enrolled in the NH 2016/17 season and 40% in the SH 2017 season.

Numbers analysed

Overall, 6,761 subjects received study treatment according to the randomization schedule (3,379 subjects received aQIV and 3382 subjects received Boostrix).

The FAS Efficacy consisted of 6,740 subjects (3,368 in the aQIV group and 3372 in Boostrix group). The PPS Efficacy consisted of 6,603 subjects (3,291 in the aQIV group and 3312 in the Boostrix group).

Outcomes

Efficacy results

Summaries of influenza-like episodes, RT-PCR confirmed influenza cases, culture-confirmed influenza cases, vaccine-matched and vaccine-unmatched culture-confirmed influenza cases are presented for both protocol-defined and modified CDC ILI in Table below.

Table 42: summary of influenza-like illness episodes and laboratory-confirmed influenza – FAS Efficacy

Episode	Strains	aQIV (N = 3368) n	Boostrix (N = 3372) n
Influenza like episode (protocol-definition)	All	801	814
Influenza like episode (modified CDC definition)	All	396	425
RT-PCR confirmed influenza - protocol-defined ILI	Any	122	151
	H1N1	4	5
	N2	96	118
	3	14	21
RT-PCR confirmed influenza - modified CDC ILI definition	Any	83	121
	H1N1	1	5
	H3N2	69	97
	B	10	16
Culture-confirmed influenza - protocol-defined ILI	Any	58	81
	H1N1	1	0
	H3N2	51	73
	B	6	8
Culture-confirmed influenza - modified CDC ILI	Any	44	66
	H1N1	1	0
	H3N2	39	61
	B	4	5
Vaccine matched culture-confirmed - protocol-defined ILI	Any	7	14
	H1N1	1	0
	H3N2	4	8
	B	2	6
Vaccine matched culture-confirmed - modified CDC ILI definition	Any	5	13
	H1N1	1	0
	H3N2	3	8
	B	1	5
Vaccine unmatched culture-confirmed - protocol-defined ILI	Any	51	67
	H1N1	0	0
	H3N2	47	65
	B	4	2
Vaccine unmatched culture-confirmed - modified CDC ILI definition	Any	39	53
	H1N1	0	0
	H3N2	36	53
	B	3	0

Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; CDC = Center for Disease Control and Prevention; FAS = Full Analysis Set; ILI = influenza-like illness; RT-PCR = Reverse Transcription Polymerase Chain Reaction.
Note 1: Primary protocol-defined ILI requires at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the symptoms: temperature of > 37.2°C/99°F, chills, tiredness, headache, or myalgia, where body temperature was collected from ILI report.
Note 2: Modified CDC ILI is defined as fever (temperature of > 37.2°C/99°F) with cough or sore throat, where body temperature was collected from both ILI report and ILI booklet.

Using the protocol defined ILI, there were 273 cases of RT-PCR confirmed influenza due to any strain. Most of these cases (214 cases) were caused by an H3N2 virus. Around 50% of RT-PCR confirmed cases

(139 cases) were culture-confirmed. 118 of these cases were due to strains antigenically unmatched (defined as ≥ 8-fold difference in titer as compared to the vaccine strain) to the vaccine strains; so only 21 cases were as matched to the strains contained in Fluad Tetra.

Primary Efficacy Objective: Vaccine Efficacy for any RT-PCR Confirmed Influenza

The efficacy of aQIV in preventing RT-PCR confirmed influenza A and/or B due to any seasonal strain was 19.80% (97.45% CI: -5.27%, 38.91%) using the protocol-defined ILI definition.

Thus, the pre-specified success criterion to demonstrate VE of aQIV was not met for the primary efficacy objective, since this criterion was that the LL of the of the two-sided 97.45% CI of VE estimate would exceed 40%. The original objective established a 95% CI but it was modified to 97.45% CI taking into account the interim analyses conducted during the trial.

Primary confirmatory objective of demonstrating the efficacy of aQIV in adults 65 years and above in protecting against any RT-PCR confirmed influenza A and/or B diseases was not met.

The results of primary efficacy objective using the PPS Efficacy (21.14% [97.45% CI: -4.36%, 40.41%]) indicated similar results as for the FAS Efficacy.

Key Secondary Efficacy Objective: Vaccine Efficacy for Influenza Antigenically Matched to the Vaccine Strains

The key Secondary Efficacy Objective was to assess VE against influenza disease caused by strains that were antigenically matched to the vaccine strains.

Protocol-defined ILI

Overall, the proportion of antigenically matched cases was low. The study did not meet the pre-specified success criteria to demonstrate the VE against culture-confirmed influenza, due to strains antigenically matched to the vaccine strains as the lower bound of the CI was not above 40%. The VE against any vaccine matched cases was 49.94% (95% CI: -24.03%, 79.79%).

Table 43: VE for antigenically matched culture-confirmed influenza (any strain and by strain) – Protocol-defined ILI – FAS Efficacy

Strain	aQIV N = 3368	Boostrix N = 3372	Absolute VE (%) (95% CI)
	Cases	Cases	
Any Strain	7	14	49.94 (-24.03, 79.79)
A/H1N1	1	0	-
A/H3N2	4	8	49.90 (-66.39, 84.91)
B/Yamagata	2	6	66.64 (-65.27, 93.27)
B/Victoria	0	0	-

Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; CI = Confidence Interval; FAS = Full Analysis Set; ILI = Influenza-Like Illness; VE = Vaccination Efficacy
Definitions: VE = (1-hazard rate of aQIV/hazard rate of Boostrix) x 100%.
Note 1: Result is based on the Cox Proportional Hazards model for time until onset of the first culture-confirmed influenza with vaccine group as the main effect.
Note 2: Matched strains are those with a < 8-fold difference in titer as compared to the vaccine strain.
Note 3: The success of the study is established if the lower limit of the two-sided 95% CI of VE estimate exceeds 40%.
Source: Table 14.2.1.5

Secondary Efficacy Objective 2: Vaccine Efficacy Against Culture Confirmed Influenza Regardless of Antigenic Match.

Protocol-defined ILI

The VE against first occurrence of culture-confirmed influenza, due to any strain regardless of antigenic match to the vaccine strains, was 28.66% (95% CI: 0.05%, 49.08%). The VE results were consistent for A/H3N2 strain (30.50% [95% CI: 0.60%, 51.41%]) and B strains (24.83% [95% CI: -116.66%; 73.92%]).

Table 44: VE for any culture-confirmed influenza (any strain and by strain) – Protocol-defined ILI – FAS Efficacy

	aQIV N = 3368	Boostrix N = 3372	Adjusted VE (%) (95% CI)
Any Strain	58	81	28.66 (0.05, 49.08)
A/H1N1	1	0	-
A/H3N2	51	73	30.50 (0.60, 51.41)
B	6	8	24.83 (-116.66, 73.92)

Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; CI = Confidence Interval; FAS = Full Analysis Set; ILI= Influenza-Like Illness; VE = Vaccination Efficacy.
Definitions: VE = (1-hazard rate of aQIV/hazard rate of Boostrix) x 100%.
Note 1: Result is based on the Cox Proportional Hazards model for time until onset of the first culture-confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects. Note that the age group is from planned stratification.
Note 2: Any strain denotes any of A/H1N1, A/H3N2, B/Yamagata and B/Victoria during the influenza season.
Note 3: B strain represents B/Yamagata or B/Victoria.
Source: Table 14.2.1.6

Secondary Efficacy Objective 3: Vaccine Efficacy Against Antigenically Unmatched Culture-confirmed Influenza.

Protocol-defined ILI

The VE against influenza disease caused by strains antigenically unmatched to the vaccine strains, was 23.79% (95% CI: -9.69%, 47.05%).

Table 45: VE for unmatched culture-confirmed influenza (any strain and by strain) – Protocol-defined ILI – FAS Efficacy

	aQIV N = 3368	Boostrix N = 3372	Adjusted VE (%) (95% CI)
Any Strain	51	67	23.79 (-9.69, 47.05)
A/H1N1	0	0	-
A/H3N2	47	65	27.61 (-5.34, 50.26)
B	4	2	-80.41 (-858.21, 66.03)

Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; CI = Confidence Interval; FAS = Full Analysis Set; ILI= Influenza-Like Illness; VE = Vaccination Efficacy.
Definitions: VE = (1-hazard rate of aQIV/hazard rate of Boostrix) x 100%.
Note 1: Result is based on the Cox Proportional Hazards model for time until onset of the first culture-confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects. Note that the age group is from planned stratification.
Note 2: Unmatched strains are those with a ≥ 8-fold difference in titer as compared to the vaccine strain.
Note 3: Note 3: B strain represents B/Yamagata or B/Victoria.
Analysis used protocol-defined ILI. Source: Table 14.2.1.7

Secondary Efficacy Objective 4: Vaccine Efficacy for RT-PCR Influenza due to any strain from 7 to 180 Days After Vaccination or at the End of Influenza Season (Early Efficacy).

Protocol-defined ILI

Overall, 303 cases of RT-PCR confirmed influenza cases occurring from 7 to 180 days or until the end of the influenza season were reported in the study and included in the FAS Early Efficacy analysis; 140 were in the aQIV group, and 163 were in the Boostrix group. The vaccine group comparison yielded an overall VE of 14.44% (95% CI: -7.25%, 31.74%).

Table 46: VE for any RT-PCR confirmed influenza occurring at ⩾ 7 days and ⩽180 days after vaccination or until the end of the influenza season – whichever is Longer – Protocol-defined ILI – FAS Efficacy

Strains	aQIV N = 3376	Boostrix N = 3376	Adjusted VE (%) (95% CI)
Any Strain	140	163	14.44 (-7.25, 31.74)

Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; CI = Confidence Interval; FAS = Full Analysis Set; ILI= Influenza-Like Illness; RT-PCR = Reverse Transcription Polymerase Chain Reaction; VE = Vaccination Efficacy.
Definitions: VE = (1-hazard rate of aQIV/hazard rate of Boostrix) x 100%.
Note 1: Result is based on the Cox Proportional Hazards model for time until onset of the first culture-confirmed influenza with vaccine group as the main effect, adjusting for age group, study site and comorbidity as random effects. Note that the age group is from planned stratification.
Note 2: Any strain denotes any of A/H1N1, A/H3N2, B/Yamagata and B/Victoria during the influenza season.
Source: Table 14.2.1.8

The success criterion of the study for the primary and key secondary efficacy objective was that the lower limit of the two-sided 95% CI of VE estimate exceeds 40%. As shown above when using the Protocol-defined ILI neither the primary nor the key secondary objective was met, as the LL of the 95% CI of VE estimates did not exceed 40%.

Modified CDC ILI definition

Similarly, when the modified CDC ILI definition was used, the success criterion of the study for the primary objective, for the key secondary efficacy objective and for the four secondary objectives was that the lower limit of the two-sided 95% CI of VE estimate exceeds 40%. In none of these cases, the success criterion was met.

Post-hoc Analyses

In addition to the analyses performed with the two prespecified ILI definitions.

- Protocol-defined ILI: At least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of >37.2°C/99°F, chills, tiredness, headache, or myalgia;
- Modified Centers for Disease Control and Prevention (CDC) ILI Definition: Fever [temperature of >37.2°C/99°F] with cough or sore throat;

A post-hoc analysis of VE was performed using the two following ILI definitions:

- Standard CDC ILI Definition (post-hoc): Fever [temperature of ≥37.8°C/100°F] with cough or sore throat (CDC 2017);
- WHO ILI Definition (post-hoc): Fever [temperature of ≥38°C/100.4°F] with cough (Fitzner 2017).

The post-hoc analyses were conducted for the primary and three secondary efficacy objectives for all subjects in relation to cases of influenza occurring from 21 through 180 days after vaccination or through the end of the influenza season, whichever was longer. Efficacy was determined based on influenza cases caused by A (H1N1 and H3N2) and either B lineages. The three secondary objectives analysed were: a) Culture-confirmed influenza antigenically matched to the vaccine strains; b) Culture-confirmed influenza regardless of antigenic match to the vaccine strains; and c) culture-confirmed influenza antigenically unmatched to the vaccine strains.

Summary of these analyses is shown in the next table.

Table 47: Study V118_18 overview of VE results – FAS Efficacy

Efficacy Endpoint	aQIV N = 3368		Boostrix N = 3372		Absolute VE (%)
	Cases, n	Attack Rate, %	Cases, n	Attack Rate, %	95% CI
Protocol-defined ILI					
RT-PCR Influenza, Any strain	122	3.6	151	4.5	19.80[a] (-5.27, 38.91)
Culture Confirmed Influenza, Any strain	58	1.7	81	2.4	**28.66[c] (0.05, 49.08)**
Culture Confirmed Influenza, Matched	7	0.2	14	0.4	49.94[b] (-24.03, 79.79)
Culture Confirmed Influenza, Unmatched	51	1.5	67	2.0	23.79[c] (-9.69, 47.05)
Modified CDC ILI					
RT-PCR Influenza, Any strain	83	2.5	121	3.6	**32.12[c] (10.23, 48.67)**
Culture Confirmed Influenza, Any strain	44	1.3	66	2.0	**33.47[c] (2.56, 54.57)**
Culture Confirmed Influenza, Matched	5	0.1	13	0.4	61.50[c] (-7.98, 86.28)
Culture Confirmed Influenza, Unmatched	39	1.2	53	1.6	26.11[c] (-11.71, 51.13)
Standard CDC ILI					
RT-PCR Influenza, Any strain	54	1.6	92	2.7	**41.87[d] (18.64, 58.46)**
Culture Confirmed Influenza, Any strain	27	0.8	50	1.5	**46.23[d] (14.13, 66.33)**
Culture Confirmed Influenza, Matched	3	0.1	9	0.3	66.61[d] (-23.32, 90.96)
Culture Confirmed Influenza, Unmatched	24	0.7	41	1.2	**41.73[d] (3.56, 64.79)**
WHO ILI					
RT-PCR Influenza, Any strain	39	1.2	79	2.3	**51.08[d] (28.21, 66.67)**
Culture Confirmed Influenza, Any strain	18	0.5	45	1.3	**60.17[d] (31.19 to 76.94)**
Culture Confirmed Influenza, Matched	2	0.1	8	0.2	74.96[d] (-17.93 to 94.68)
Culture Confirmed Influenza, Unmatched	16	0.5	37	1.1	**57.02[d] (22.73 to 75.95)**

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; ILI = influenza-like illness; CDC = Centers for Disease Control and Prevention; CI = confidence interval; FAS = Full Analysis Set; N = total number of subjects; n = number of subjects included in the subset; RT-PCR = reverse transcriptase-polymerase chain reaction; VE = vaccine efficacy.

Notes: a Primary objective of the study (tested at alpha level of 2.55% after adjusting for interim analysis); b Key secondary objective; c Secondary objective; d Post-hoc analysis.
Protocol-defined ILI: At least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/ 99°F, chills, tiredness, headache, or myalgia.
Modified CDC ILI definition: Fever (temperature of > 37.2° C/99°F) with cough or sore throat.
Standard CDC ILI definition: Fever (temperature of ≥ 37.8° C/100°F) with cough or sore throat.
WHO ILI definition: Fever (temperature of ≥ 38° C/100.4°F) with cough.
Bold = a lower bound of the 95% CI > 0.

An important observation in study V118_18 was that the clinical criteria used to define ILI appeared to have an impact on the estimated efficacy of aQIV. Three definitions of ILI were used for the statistical

analysis of this study and included in the CSR. The primary protocol definition of ILI required the presence of at least 1 respiratory and at least 1 systemic symptom and was used to identify potential cases of influenza during the surveillance period of the study, but did not require the presence of fever. This was consistent with another influenza vaccine efficacy study conducted in this age population (Diaz Granados et al. 2014) and represents the most sensitive definition of influenza. Cases defined in this way that were confirmed by RT-PCR are likely to include milder disease with limited symptomatology. In contrast, the secondary 'modified CDC' and post-hoc 'standard Centers for Disease Control and Prevention (CDC)' definitions of ILI, which required presence of fever >37.2°C or ≥37.8°C, respectively, with cough or sore throat, are less sensitive, but more specific for clinical significant influenza disease. Moreover, the addendum to the CSR includes a fourth post-hoc analysis using the WHO ILI definition (fever ≥38.0 °C with cough) as the most specific definition of influenza infection. (Casalegno et al. 2017). Efficacy of aQIV was 19.80% [95% CI -5.27, 38.91] using the protocol-specified ILI definition, 32.1% [95% CI 10.23, 48.67] using the modified CDC ILI definition, 41.87% [95% CI 18.64, 58.46] using the standard CDC ILI definition, and 51.08% [95% CI 28.21, 66.67] using the WHO ILI definition (CSR V118_18).

In summary, aQIV showed moderate vaccine efficacy against RT-PCR-confirmed and culture-confirmed influenza in adults 65 years of age and above. Although the V118_18 study did not meet the primary and key secondary efficacy objectives, the study results show reasonable protection during influenza seasons with an antigenic mismatch between the circulating and vaccine influenza strains. The observed efficacy of aQIV in V118_18 is in line with the effectiveness estimates for licensed influenza vaccines (15% to 38%), obtained during the same influenza seasons (Flannery 2019; Rondy 2017; Sullivan 2017). aQIV provided statistically significant protection against more clinically relevant influenza disease (influenza cases associated with a higher fever as shown by results using the standard CDC and WHO ILI definitions). These results indicate that aQIV may prevent more severe and clinically relevant influenza cases, which is particularly important in this vulnerable elderly population where the medical and economic burden of influenza illness is high (Smetana 2018; Matias 2017).

Immunogenicity results

Evaluation of the immunogenicity objectives was done in the immunogenicity sub-cohort of subjects. The primary analysis was based on the FAS Immunogenicity and a complementary analysis, was also performed on the PPS Immunogenicity since more than 5% of subjects were excluded from the PPS analysis. The FAS cohort for immunogenicity consisted of 1656 subjects (1324 in the aQIV group and 322 in the Boostrix group).

The immunogenicity endpoints were assessed at baseline (Day 1) and 3 weeks after the study vaccination (Day 22) using HI assay. The Geometric Mean Titers (GMT) and Geometric Mean Ratios (Day 22/Day 1) (GMR) results are presented in the following Table

Table 48: GMT on Day 1 and Day 22 and GMR (Day22/Day1) of HI – FAS Immunogenicity

Strain		aQIV N = 1324	Boostrix N = 332
		GMT or GMR (95% CI)	GMT or GMR (95% CI)
A/H1N1	GMT Day 1	31.86 (28.49, 35.63)	36.19 (30.05, 43.57)
	GMT Day 22	438.79 (403.82, 476.79)	29.43 (25.63, 33.79)
	GMR Day 22/Day 1	14.17 (12.84, 15.64)	0.89 (0.76, 1.05)
A/H3N2	GMT Day 1	28.31 (25.43, 31.52)	27.56 (23.05, 32.95)
	GMT Day 22	572.80 (525.08, 624.86)	27.06 (23.42, 31.25)
	GMR Day 22/Day 1	22.65 (20.48, 25.06)	1.08 (0.92, 1.28)
B/Yamagata	GMT Day 1	13.83 (12.81, 14.92)	13.13 (11.57, 14.91)
	GMT Day 22	86.77 (79.94, 94.19)	12.49 (10.90, 14.30)
	GMR Day 22/Day 1	6.58 (6.02, 7.20)	0.97 (0.84, 1.13)
B/Victoria	GMT Day 1	12.77 (11.81, 13.81)	12.26 (10.77, 13.96)
	GMT Day 22	104.26 (95.77, 113.50)	11.25 (9.77, 12.94)
	GMR Day 22/Day 1	8.59 (7.83, 9.42)	0.94 (0.81, 1.10)

Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; CI = Confidence Interval; FAS = Full Analysis Set; GMR = Geometric Mean Ratio Day 22/Day 1; GMT = Geometric Mean Titer; HI = Hemagglutination Inhibition.
Statistical model used: PROC GLM log titer = arm age group 'log titer (Day 1)' comorbidity country.
Note 1: age group is from planned stratification.
Note 2: Adjusted GMT, GMR, and 95% CI are analyzed using analysis of covariance (ANCOVA) with covariates as specified in the model above.
Source: Table 14.2.1.1.

The GMT and GMR results show that:

• The GMTs at Day 1 were generally similar between the two vaccine groups for all strains (12.77 to 31.86 for the aQIV group and 12.26 to 36.19 for the Boostrix group).

• At Day 22, post-vaccination HI GMTs for the aQIV group were 438.79 (A/H1N1), 572.80 (A/H3N2), 104.26 (B/Victoria) and 86.77 (B/Yamagata), compared to 29.43, 27.06, 11.25, and 12.49, respectively, for the Boostrix group.

• GMRs (Day 22/Day 1) obtained for the aQIV group (14.17 [A/H1N1], 22.65 [A/H3N2], 8.59 [B/Victoria] and 6.58 [B/Yamagata]) were significantly higher than those for Boostrix group (0.89, 1.08, 0.94, and 0.97, respectively).

Percentages of Subjects Who Achieved Seroconversion.

Table 50The table below summarizes the proportion of subjects who achieved seroconversion post-vaccination at Day 22 in the FAS Immunogenicity.

Table 49: Number (%) of subjects with HI titer seroconversion at Day 22 – FAS Immunogenicity

Strain	aQIV (N = 1324)	Boostrix (N = 332)
	Seroconversion Day 22 (% [95% CI])	
A/H1N1	78.0% (**75.66%**, 80.21%)	2.1% (0.85%, 4.31%)
A/H3N2	84.6% (**82.52%**, 86.49%)	3.9% (2.11%, 6.62%)
B/Yamagata	60.8% (**58.06%**, 63.41%)	3.6% (1.89%, 6.27%)
B/Victoria	65.5% (**62.88%**, 68.10%)	2.1% (0.85%, 4.31%)

Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; CBER = Center for Biologics Evaluation and Research; CI = Confidence Interval; HI = Hemagglutination Inhibition.
Unadjusted estimates for individual vaccine group estimates reported with Clopper Pearson CIs. Unadjusted estimates for vaccine group difference reported with Miettinen-Nurminen confidence intervals.
Percentage = Number/N, N is the number of subjects in the corresponding visit and arm.
CBER criteria is achieved if the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody seroconversion met or exceeded 30%.
Seroconversion is defined as HI titer ≥1:40 for subjects sero-negative at baseline (HI titer <1:10); or a minimum 4-fold increase in HI titer for subjects sero-positive at baseline (HI titer ≥1:10) on Day 22.
Source: Table 14.2.1.3

The pre-specified CBER criteria for sufficiency of immune response were achieved for all four strains in the aQIV group as the LL of the two-sided 95% CI for the proportion of subjects achieving an HI antibody seroconversion exceeded 30%.

2.5.4.4. Summary of main studies

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

Table 50: Summary of efficacy for trial V118_20

Title: a Phase 3, Randomized, Double-Blind, Controlled, Multicenter, Clinical Study to Evaluate Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Subunit Influenza Vaccine in Comparison With an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine and an MF59-Adjuvanted Trivalent Subunit Influenza Vaccine Containing the Alternate B Strain, in Adults Aged 65 Years and Above.			
Study identifier	V118_20		
Design	Randomised, double-blinded, comparator-controlled, multicentre study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Day (vaccination) through 22 days not applicable not applicable	
Hypothesis	Non-inferiority, superiority		
Treatments groups	aQIV (Adjuvanted quadrivalent Influenza vaccine)		A/ Michigan/45/2015 (H1N1)-like virus A/ Hong Kong/4801/2014 (H3N2)-like virus B/ Phuket/3073/2013-like (Yamagata lineage) B/ Brisbane/60/2008-like (Victoria lineage) MF59 number randomized: 889
	aTIV-1 (Fluad Adjuvanted trivalent influenza vaccine-1)		A/ Michigan/45/2015 (H1N1)-like virus A/ Hong Kong/4801/2014 (H3N2)-like virus B/ Brisbane/60/2008-like (Victoria lineage) MF59 number randomized: 445
	aTIV-2 (Adjuvanted trivalent influenza vaccine-2)		A/ Michigan/45/2015 (H1N1)-like virus A/ Hong Kong/4801/2014 (H3N2)-like virus B/ Phuket/3073/2013-like (Yamagata lineage) MF59 number randomized: 444
Endpoints and definitions	First Co-Primary endpoint	**GMT ratio** (geometric mean titer) **SCR difference** (seroconversion rate)	Non-inferiority of aQIV compared to aTIV-1 and to aTIV-2 to the 4 strains included in the vaccine measured by haemagglutinin Inhibition antibody titers as GMTr and SCR difference on day 22
	Secondary endpoint	**GMT ratio** (geometric mean titer) **SCR difference** (seroconversion rate)	Comparison of aQIV versus aTIV-1/aTIV-2 for the alternate B strain (the influenza B strain included in aQIV but not in aTIV-1 or aTIV-2) measured by the HI antibody titers as GMTr and SCR difference on day 22.
Database lock	June 13, 2018		

Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Per protocol Set D22 Adjusted GMTs				
Descriptive statistics and estimate variability	Treatment group	aQIV	aTIV-1	aTIV-2	
	Number of subject	872	436	433	
	A/H1N1 GMT D22 (95% CI)	65.01 (57.79,73.13)	75.16 (66.68, 84.72)		
	A/H3N2 GMT D22 (95% CI)	294.91 (261.88, 332.09)	293.31 (259.91, 330.99)		
	B/Yam GMT D22 (95% CI)	24.67 (22.67, 26.84)	15.96 (14.48, 17.59)	24.30 (22.00, 26.84)	
	B/Vic GMT D22 (95% CI)	30.78 (28.27, 33.51)	30.13 (27.31, 33.24)	21.80 (19.73, 24.09)	
	A/H1N1 SCR (95%CI)	35.21 (32.03, 38.48)	pooled 38.43 (35.19, 41.76)		
	A/H3N2 SCR (95%CI)	39.33 (36.08, 42.67)	pooled 39.70 (36.43,43.04)		
	B/Yam SCR (95%CI)	16.40 (14.00, 19.03)	4.59 (2.82, 7.00)	15.47 (12.20, 19.23)	
	B/Vic SCR (95%CI)	13.42 (11.22, 15.86)	12.16 (9.24, 15.60)	2.77 (1.44, 4.79)	
Effect estimate per comparison	First Co Primary endpoint	Comparison groups	GMT ratio aTIV/aQIV		
		GMT ratio (95%CI)	A/H1N1 A/H3N2 B/Yam B/Vic	1.16 (1.05, **1.27**) 0.99 (0.90, **1.09**) 0.99 (0.90, **1.08**) 0.99 (0.90, **1.08**)	
		Prespecified noninferiority criteria: upper bound of two-sided 95% CI for GMT ratios (aTIV/aQIV) for all four homologous strains < 1.5			
		Comparison groups	SCR differences aTIV-aQIV		
		SCR difference (95%CI)	A/H1N1 A/H3N2 B/Yam B/Vic	3.23 (-1.30, **7.76**) 0.37 (-4.23, **4.96**) -0.93 (-5.13, **3.27**) -1.26 (-5.07, **2.55**)	
		Prespecified noninferiority criteria: upper bound of the 95% CI of the intergroup difference for SCR (aTIV minus aQIV) for all four homologous strains < 10%			
Secondary endpoint	Comparison of aQIV relative to aTIV for the Alternate B Strain				
Analysis population and time point description	Full analyses Set D22 Adjusted GMTs				

Descriptive statistics and estimate variability	Treatment group	aQIV	aTIV-1	aTIV-2
	Number of subject	886	443	441
	B/Yam GMT D22 (95% CI)	24.81 (22.80,27.00)	24.81 (22.80, 27.00)	24.59 (22.27, 27.16)
	B/Vic GMT D22 (95% CI)	31.02 (28.50, 33.76)	30.22 (27.41, 33.33)	21.94 (19.87, 24.24
	B/Yam SCR (95%CI)	16.70 (14.31, 19.33)	4.74 (2.96, 7.16)	15.65 (12.38, 19.38)
	B/Vic SCR (95%CI)	13.54 (11.36, 15.98)	11.96 (9.09, 15.36)	2.72 (1.41, 4.70)

Effect estimate per comparison	Secondary endpoint	Comparison groups	GMT ratio aTIV/aQIV	
		GMT ratio (95%CI)	B/Yam aTIV-1 B/Vic aTIV-2	0.64 (0.58, **0.70**) 0.71 (0.64, **0.78**)
		Prespecified superiority criteria: upper bound of two-sided 95% CI for GMT ratios (aTIV/aQIV) for all four homologous strains < 1		
		Comparison groups	SCR differences aTIV-aQIV	
		SCR difference (95%CI)	B/Yam aTIV-1 B/Vic aTIV-2	-11.96 (-15.12, **-8.81**) -10.82(-13.54, **-8.11**)
		Prespecified superiority criteria: upper bound of the 95% CI of the intergroup difference for SCR (aTIV minus aQIV) for all four homologous strains < 0%		

Table 51: Summary of efficacy for trial V70_27

Title: A Phase 3, Randomized, Controlled, Observer-Blind, Multicenter Study to Evaluate the Safety and Immunogenicity and the Consistency of Three Consecutive Lots of a MF59C.1 Adjuvanted Trivalent Subunit Influenza Vaccine in Elderly Subjects Aged 65 Years and Older.		
Study identifier	V70_27	
Design	Randomized, observer-blinded, comparator-controlled, multicentre study, phase III	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Day (vaccination) through 22 days and day 366 not applicable not applicable
Hypothesis	superiority	
Treatments groups	aTIV (TIV-ADJ, Fluad)	A/California/7/2009 (H1N1)-like strain A/Perth/16/2009 (H3N2)-like strain B/Brisbane/60/2008-like strain Adjuvant MF59 number randomized: 3552, vaccinated 3541
	TIV (TIV-NONADJ, Agrippal)	A/California/7/2009 (H1N1)-like strain A/Perth/16/2009 (H3N2)-like strain B/Brisbane/60/2008-like strain number randomized: 3552, vaccinated 3541

Endpoints and definitions	Primary endpoint	**GMT ratio** (geometric mean titer) **SCR difference** (seroconversion rate)	Superiority of aTIV compared to TIV for at least 2 homologous strains in all subjects as measured by GMT ratios and seroconversion rate differences at day 22.
	Secondary endpoint	**GMT ratio** (geometric mean titer) **SCR difference** (seroconversion rate)	Comparison of aTIV compared to TIV for at least 2 heterologous strains in all subjects as measured by GMT ratios and seroconversion rate differences at day 22.
	Secondary endpoint	**GMT ratio** (geometric mean titer) **SCR difference** (seroconversion rate)	Comparison of aTIV to TIV for homologous antibody persistence in a subset of subjects as measured by GMT ratios and seroconversion rate differences at day 366.
Database lock	29 Nov 2011		

Results and Analysis

Analysis description	**Primary Analysis homologous strain**		
Analysis population and time point description	Full analysis set D22 Adjusted GMTs (day 1 titre, country, age cohort)		
Descriptive statistics and estimate variability	Treatment group	aTIV (TIV-ADJ)	TIV (TIV-NONADJ)
	Number of subject	3479	3482
	A/H1N1 GMT D22 (95% CI)	98 (92-104)	71 (67-76)
	A/H3N2 GMT D22 (95% CI)	267 (253-282)	167 (158-176)
	B/Vic GMT D22 (95% CI)	27 (26-29)	24 (23-25)
	A/H1N1 SCR (95%CI)	68% (67%-70%)	59% (57%-60%)
	A/H3N2 SCR (95%CI)	72% (71%-74%)	58% (56%-60%)
	B/Vic SCR (95%CI)	33% (31%-34%)	30% (28%-31%)

Effect estimate per comparison	Primary endpoint	Comparison groups	GMT ratio (aTIV/TIV)	
		GMT ratio (95%CI)	A/H1N1 A/H3N2 B/Vic	1.37(1.29-1.46) 1.6 (**1.51**-1.68) 1.14(1.08-1.2)
		Multiplicity adjusted P-value superiority	A/H1N1 A/H3N2 B/Vic	1.000 0.055 1.000
		Superiority criterion: lower bound of 95% CI for GMT ratios (aTIV/TIV) ≥ 1.5 for at least 2 of the 3 strains		
		Comparison groups	SCR differences (aTIV-TIV)	
		SCR difference (95%CI)	A/H1N1 A/H3N2 B/Vic	9.6% (7.4%-11.8%) 13.8% (**11.7%**-16%) 3% (1%-5%)
		Multiplicity adjusted P-value superiority	A/H1N1 A/H3N2 B/Vic	1.000 0.002 1.000
		Superiority inferiority criterion: lower bound of the 95% CI of the difference for SCR (aTIV-TIV) >10% for at least 2 of the 3 strains		

Table 52: Summary of efficacy for trial V118_18

Title: A Phase III, Randomized, Observer-Blind, Controlled, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared to Non-influenza Vaccine Comparator in Adults ≥ 65 Years of Age.		
Study identifier	V118_18 IND number: 15684 EudraCT: 2015-000728-27	
Design	The purpose of this study is to demonstrate the efficacy, safety and immunogenicity of an MF59-adjuvanted inactivated egg-derived quadrivalent influenza vaccine (aQIV) in preventing seasonal influenza in elderly adults. This randomized, observer-blind, non-influenza vaccine comparator-controlled study was intended to demonstrate that aQIV prevents Reverse Transcription Polymerase Chain Reaction (RT-PCR) confirmed influenza.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment phase: day 1 to day 22 Safety follow-up phase: 12 months not applicable not applicable
Hypothesis	Absolute efficacy (clinical protection)	
Treatments groups	aQIV	Quadrivalent influenza vaccine adjuvanted with MF59C.1, containing 15 µg of hemagglutinin (HA) of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 µg of HA in the vaccine. Number randomized: 3381 subjects

	Boostrix		Combined Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed Number randomized: 3380 subjects
Endpoints and definitions	Primary efficacy endpoint		Time to first occurrence of RT-PCR confirmed influenza from 21 through 180 days after vaccination or end of the influenza season, whichever was longer.
	Primary safety endpoint 1, 2 and 3		Safety objective 1 was assessed by calculating the percentage of subjects in the solicited safety subset with solicited local and systemic AEs from Day 1 through Day 7. Safety objectives 2 and 3 were assessed based on: • Percentage of subjects with medically attended AEs within 30 days after of first occurrence RT-PCR confirmed ILI. • Percentages of subjects with any unsolicited AE and concomitant medication reported from Day 1 through Day 22. • Percentages of subjects with SAEs, AEs leading to withdrawal from the study, NOCD, AESI reported from Day 1 to Day 366 and all concomitant medications associated with these events.
	Secondary	Efficacy	Efficacy endpoints were assessed based on antigenic match of culture isolated influenza to the strains of virus contained in the seasonal vaccine
	Secondary	Immunogenicity	HI assay against homologous strains at Days 1 and 22 in terms of GMTs, GMRs, SCR
	Exploratory	Immunogenicity	Determined by the MN assay against homologous strains at Days 1 and 22
	Exploratory	Post-hoc efficacy	Time to first occurrence of RT-PCR confirmed influenza from Day 21 to Day 180 after vaccination or end of the influenza season, whichever was longer using the standard CDC ILI definition.
Database lock	September 18, 2018		

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**
Analysis population and time point description	Full Analysis Set (FAS) Efficacy: Subjects in the All Enrolled Set who were randomized and received a study treatment, were under observation for at least 21 days post-vaccination and provided efficacy data.
Descriptive statistics and estimate variability	*Primary efficacy objectives:* Primary and key secondary VE data were analyzed using the FAS Efficacy and PPS Efficacy sets. All non-key secondary VE objectives were analyzed using FAS Efficacy and repeated on PPS. <u>Primary and Secondary Efficacy Objectives</u>:

	The primary measure of absolute efficacy was tested in elderly subjects ⩾ 65 years of age according to the following null (H0) and alternative (H1) hypothesis: H0: 1- HR = VE ⩽ 0.4 versus H1: VE > 0.4 Where HR is the hazard ratio of the incidence of protocol-defined ILI in aQIV versus a non-influenza comparator estimated by the proportional hazards model and VE is vaccine efficacy. One interim analysis was performed. To control the overall type 1 error alpha ⩽ 0.05, the CIs for the final analysis of primary efficacy objective were adjusted accordingly. The primary efficacy and key secondary efficacy objectives were considered achieved if the lower limit (LL) of the adjusted two-sided 95% CI of absolute VE exceeded 40%. Post-hoc Analysis: VE using the standard CDC ILI Definition: VE estimates were calculated using similar analyses as the primary and secondary efficacy objectives. <u>Immunogenicity</u>: Immunogenicity data were analyzed using FAS Immunogenicity and repeated using PPS Immunogenicity if more than 5% of subjects were excluded from FAS Immunogenicity. All statistical analyses for HI titers were performed on the logarithmically (base 10) transformed values. Individual HI titers below detection limit (< 10) were set to half of that limit (5). Crude estimates for GMTs, GMRs and pertaining two-sided 95% CIs were calculated assuming lognormal distribution of the titers and were completed by providing minimum, maximum and median titers for each vaccine group. Binary data (i.e., percentages of subjects with seroconversion and with titer ⩾ 1:40) were summarized for each group using unadjusted estimates and was reported together with two-sided 95% CIs. Immunogenicity endpoints at Day 22 were assessed according to the criteria for sufficient immune response described in Center for Biologics Evaluation and Research (CBER) Guidance 'Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines' (2007) states the following: • The lower limit (LL) of the two-sided 95% confidence intervals (CI) for the percent of subjects achieving seroconversion for HI antibody should have met or exceeded 30%. • The LL of the two-sided 95% CI for the percent of subjects who achieved an HI antibody titer ⩾ 1:40 should have met or exceeded 60%.

Primary endpoint results	**Efficacy Results** In total, 273 cases of RT-PCR confirmed influenza due to any strain were reported in the study; 122 were in the aQIV group, and 151 were in the comparator group. Of 273 RT-PCR-confirmed cases, 214 cases were caused by influenza A/H3N2 virus, 35 cases by B strains, 9 cases by A/H1N1 strain. In total, 139 of the 273 influenza cases were culture-confirmed, and 21 of the 273 influenza cases were defined as matched to the strains contained in the aQIV vaccine. *Primary Efficacy Objective:* • The efficacy of aQIV in preventing RT-PCR confirmed influenza A and/or B due to any seasonal strain was 19.80% (97.45% CI: -5.27%, 38.91%) using the protocol-defined ILI definition. • Greater VE was observed using the modified CDC ILI definition; the efficacy of aQIV in preventing RT-PCR confirmed influenza due to any strain was 32.12% (95% CI: 10.23%, 48.67%). • Greater VE was obtained during the NH 2016/17 influenza season as compared to the SH 2017. The VE for any strain detected by RT-PCR using the protocol-defined ILI was 26.60% (95% CI: 0.60%, 45.80%) for the NH 2016/17 season versus 7.27% (95% CI: -36.76%, 37.12%) in the SH 2017 season. In summary, the majority of influenza cases were caused by A/H3N2 strains and were antigenically unmatched to the vaccine strain. The pre-specified success criterion to demonstrate efficacy of aQIV against any RT-PCR confirmed influenza (the primary objective) was not met as the LL of the 95% CI of VE estimate did not exceed 40%. The pre-specified success criterion to demonstrate efficacy of aQIV against culture-confirmed influenza due to antigenically matched strains (the key secondary objective) was also not met given the low number of matched cases, as the LL of the 95% CI of VE estimates did not exceed 40%. aQIV provided higher VE estimates, with lower bounds above zero when the modified CDC ILI and standard CDC ILI definitions were used. **Immunogenicity Results:** Immunogenicity was assessed using HI assay at baseline (Day 1) and post-vaccination (Day 22) in a subset of subjects. aQIV elicited a robust post-vaccination immune response against all four strains contained in the vaccine. <u>GMTs:</u> • At Day 1, GMTs were generally similar between the two vaccine groups for all strains (12.77 to 31.86 for the aQIV group and 12.26 to 36.19 for the Boostrix group). • At Day 22, post-vaccination HI GMTs for the aQIV group were 438.79 (A/H1N1), 572.80 (A/H3N2), 104.26 (B/Victoria) and 86.77 (B/Yamagata),

	compared to 29.43, 27.06, 11.25, and 12.49, respectively, for the Boostrix group. GMRs: • GMRs (Day 22/Day 1) obtained for the aQIV group (14.17 [A/H1N1], 22.65 [A/H3N2], 8.59 [B/Victoria] and 6.58 [B/Yamagata]) were significantly higher than those for Boostrix group (0.89, 1.08, 0.94, and 0.97, respectively). Percentage of subjects with HI titer ⩾ 1:40: • At Day 1, the percentage of subjects with HI titers ⩾ 1:40 were similar in both the vaccine groups (21.2 to 49.7% for the aQIV group and 18.7 to 50.5% for the Boostrix group). • At Day 22, post-vaccination, a significantly higher proportion of subjects achieved seroconversion in the aQIV group (96.2% [A/H1N1], 95.6% [A/H3N2], 81.6% [B/Victoria], and 79.2% [B/Yamagata]) as compared to the Boostrix group (46.7%, 41.7%, 18.4%, and 21.5%, respectively). The CBER criteria were achieved for all four strains in the aQIV group at Day 22 (LL of the 95% CI for proportion of subjects with HI antibody titer ⩾ 1:40 was > 60%). Seroconversion: • A higher proportion of subjects achieved seroconversion in the aQIV group (78.0% [A/H1N1], 84.6% [A/H3N2], 65.5% [B/Victoria], and 60.8% [B/Yamagata]) as compared to the Boostrix group (2.1%, 3.9%, 2.1%, and 3.6%, respectively). • The CBER criteria were achieved for all four strains in the aQIV group at Day 22 (LL of the 95% CI the proportion of subjects achieving an HI antibody seroconversion exceeded 30%). Subgroups (age, comorbidity status, previous vaccination, gender, and race): • Subgroup analyses confirmed adequate immune response of aQIV in subjects of different age groups (⩾ 65-74, ⩾ 75-84, ⩾ 85 years), comorbidity status, previous influenza vaccination history, gender and race. In summary, aQIV elicited a robust immune response against all four strains contained in the vaccine which met CBER criteria of sufficient immunogenicity for this age group
Analysis description	**Secondary analysis**
Analysis population and time point description	The Statistical Analysis Plan provides the description of the analysis for the active study period and safety follow-up through to the final evaluation (12 months following last study vaccination dose), sample size, and power considerations. Per Protocol Set (PPS) for Efficacy/Immunogenicity analysis includes subjects who: • Correctly received the vaccine (i.e., received the vaccine to which the subjects were randomized to receive). • Had no Clinical Study Report (CSR)-reportable protocol deviation leading to exclusion as defined prior to unblinding. • Were not excluded due to other reasons defined prior to unblinding.

Descriptive statistics and estimate variability	Success Criterion for Key Secondary Efficacy Objective The key secondary objective was achieved if the LL of the two-sided 95% CI of absolute VE estimate was > 0.4. As for the primary efficacy objective, the CI level was to be adjusted to reflect adjustment of type 1 error in case of an interim analysis. Success Criteria for Secondary Immunogenicity Objectives The endpoints of percent of subjects achieving seroconversion and HI titer ⩾ 1:40 at Day 22 were assessed against the criteria described in CBER Guidance Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (2007): • The LL of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30%. • The LL of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 60%.
Secondary endpoint results	Key Secondary Efficacy Objective 1: • A low number of influenza cases met the definition as antigenically matched to the vaccine strain; 21 of the 273 influenza cases. • The point estimate for efficacy of aQIV in prevention of culture-confirmed influenza A and/or B due to antigenically-matched vaccine strains was in the expected range (VE of 49.94% [95% CI: -24.03%, 79.79%] for the protocol-defined ILI and 61.50% [95% CI: -7.98%, 86.28%] for modified CDC ILI). Secondary Efficacy Objective 2: • The efficacy of aQIV in preventing culture-confirmed influenza A and/or B due to any strain was consistent with the results obtained for any RT-PCR confirmed influenza: VE of 28.66% (95% CI: 0.05%, 49.08%) for the protocol-defined ILI and 33.47% (95% CI: 2.56%, 54.57%) for modified CDC ILI. Secondary Efficacy Objective 3: • The efficacy of aQIV in preventing culture-confirmed influenza A and/or B due to antigenically unmatched strains was 23.79% (95% CI: -9.69%, 47.05%) for the protocol-defined ILI and 26.11% (95% CI: -11.71%, 51.13%) for modified CDC ILI definition. Greater VE was obtained during the NH 2016/17 influenza season as compared to the SH 2017: 42.10% (95% CI: 7.72%, 63.67%) for the NH 2016/17 and -22.13% (95% CI: -124.23%, 33.48%) for the SH 2017, for protocol-defined ILI. Secondary Efficacy Objective 4: • The efficacy of aQIV against any RT-PCR confirmed influenza during the period from 7 days to 180 days after vaccination was in the same range as the estimate obtained as from 21 days to 180 days post-vaccination: 14.44% (95% CI: -7.25%, 31.74%).

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trial V118_20	aQIV / aTIV-1 and aTIV-2	aQIV / aTIV-1 and aTIV-2	aQIV / aTIV-1 and aTIV-2
	602 / 596	239 /245	31 / 28
Controlled Trial V118_18	aQIV / Boostrix	aQIV / Boostrix	aQIV / Boostrix
	2416/2406	893/928	85/62
Non controlled trials	Not applicable	Not applicable	Not applicable

2.5.5. Supportive studies (elderly indication)

This section summarizes immunogenicity results from the 7 supportive studies that compare immunogenicity of a single dose of aTIV versus TIV. There were also two open label noninterventional studies comparing aTIV versus TIV, which were not sponsored by the Applicant, but that will also be commented. The summary provided for each study is based on the primary analysis population prespecified in the protocol and its accompanying SAP; this was typically the PPS, unless specified otherwise.

The 7 supportive studies evaluated different aspects of the immunogenicity of aTIV versus TIV: immunogenicity as determined by HI assay at baseline and at approximately 3-4 weeks postvaccination against homologous or heterologous strains, antibody persistence at 6 months postvaccination, immunogenicity (homologous or heterologous strains) as determined by microneutralization (MN) assay, cell mediated response (CMI) to vaccination with aTIV and immunogenicity in subjects receiving up to 3 consecutive (annual) vaccinations.

The two open label noninterventional studies comparing aTIV versus TIV were conducted to assess the relative risk (RR) of hospitalizations for influenza disease or pneumonia (C70P1 conducted in Italy) and to assess vaccine effectiveness for influenza disease (V70_49OBTP conducted Canada).

The summary table of immunogenicity results provided for many of the 7 studies below refers to the criteria established in 1996 by the CHMP (CPMP/BWP/214/96) which were current at the time of conduct of the studies. While some of these studies were conducted prior to the criteria coming into force, immunogenicity results for endpoints corresponding to each criterion were included in each of the 7 studies; therefore, these results were used to provide an objective and standardized assessment of the immunogenicity of aTIV.

A summary of the immunogenicity results of the 7 supportive studies follows. Overall, there was a trend of greater immunogenicity in adjuvanted vaccine (aTIV) groups compared to nonadjuvanted vaccine (TIV) groups across all supportive studies in terms of GMTs at approximately 3 weeks after vaccination, GMRs, and SCRs.

Immune response after revaccination

Five of the supportive studies (V7P3, V7P5, V7P7, V7P8 and V7P25), evaluated the immunogenicity after revaccination with aTIV versus revaccination with TIV. Subjects received a second and even a third annual injection with the same vaccine received approximately 1 year (or two years) earlier in the corresponding study that compared aTIV with TIV.

Overall, the responses obtained in the aTIV groups were higher than those from the TIV groups, but not in all cases and in all strains. In any case, the antibody response in the subjects that received aTIV was at least non-inferior to the response in the subjects that received TIV.

Effectiveness studies with aTIV

The applicant submitted two publications regarding vaccine effectiveness of aTIV instead of two clinical study reports. Based upon these publications claims in section 5.1 are made.

Study C70P1

Study C70P1 was a noninterventional prospective cohort study performed in the 5 Northern Italian health districts during the 2006/2007, 2007/2008 and 2008/2009 influenza seasons (Mannino et al 2012).

The study objectives were to assess the relative risk of hospitalizations for influenza or pneumonia during the influenza season amongst subjects ≥65 years of age who received either aTIV or nonadjuvanted TIV. The choice of influenza vaccine for each study subject, either aTIV or TIV (Agrippal), was left to the individual provider to be determined on the basis of local influenza vaccination policy.

The study outcome was defined as a hospital discharge diagnoses for influenza or pneumonia at least 3 weeks following vaccination during defined periods of the influenza season based on the epidemic curves of the national influenza surveillance. The primary analysis was based on outcomes occurring during and including adjacent weeks to the peak of the influenza season. Laboratory based confirmation of influenza was not available.

Over the 3 influenza seasons, the study enrolled 107,661 subjects of ≥65 years of age, with 43,667 subjects participating for more than 1 year. Overall, 170,988 vaccinations were administered by the subjects' health care providers comprising of 88,449 doses of aTIV and 82,539 doses of TIV. Due to local immunization policy, subjects who received aTIV had worse baseline health status than those subjects who received TIV. After adjusting for confounding variables (baseline health status, others), the risk of hospitalization for influenza or pneumonia was 25% lower for aTIV relative to TIV (relative risk = 0.75, 95% CI: 0.57-0.98). Outside of the influenza season, the baseline risk of hospitalization was higher for aTIV than for TIV recipients indicating that the analysis had not removed all confounding. To the extent that there is residual bias, this would suggest the true protective effect of aTIV would be even stronger.

Study V70_49OBTP

Study V70_49OBTP was a noninterventional study using a test-negative design to estimate vaccine effectiveness of aTIV versus a nonadjuvanted TIV (standard TIV predominantly Fluviral), or no vaccination in subjects ≥65 years of age in three Canadian Health Authorities.

Cases were defined as patients with ILI who were influenza polymerase chain reaction (PCR) positive, and controls were defined as patients with ILI but who were influenza PCR-negative as analyzed at a central provincial laboratory. In total, 282 subjects (84 cases and 198 controls) were enrolled among whom 227 subjects had received routine vaccination, comprising of 165 subjects vaccinated with aTIV, 62 with a nonadjuvanted TIV and 55 non-vaccinated subjects. The majority of the participants reported at least a one chronic disease (89%). The most commonly reported chronic diseases categories were cardiac (72%) followed by neurological (39%) and respiratory condition (30%). After adjustment for confounding variables (age, sex, residency in long-term care facility, chronic conditions, region and week

of testing), the absolute vaccine effectiveness for aTIV was 58% (95% CI: 5%, 82%; P < 0.04) whereas nonadjuvanted TIV was ineffective compared to no vaccination. The relative vaccine effectiveness for aTIV was 63% (95% CI: 4%, 86%; P = 0.04) as compared to nonadjuvanted TIV.

Concomitant administration

To support concomitant administration of aTIV with PPSV23 and PCV13 two publications were included in the literature references.

PPSV23

Song et al, Immunogenicity and safety of concomitant MF59-adjuvanted influenza vaccine and 23-valent pneumococcal polysaccharide vaccine administration in elderly. Vaccine 33 (2015) 4647-4652.

In this study, subjects aged ≥65 years (N = 224) were randomized 1:1:1:1 to receive aTIV alone, aTIV + 23-valent pneumococcal polysaccharide vaccine (PPSV23) in contralateral arms, aTIV + PPSV23 in the same arm or PPSV23 alone. HI assays were used to evaluate the response for the influenza antigens. Validated multiplex opsonophagocytic killing assay (MOPA) was used to evaluate the response against pneumococcal antigens. Target strains (expressing capsule types 5, 6B, 18C and 19A, respectively) were derived from wild-type strains. HI antibody titres and OIs were expressed as geometric means with 95% confidence intervals. Non-inferiority was defined as met if the lower limit of the two-sided 95% CI for the GMT ratio [(aTIV + PPSV23)/PPSV23 or (aTIV + PPSV23)/aTIV] at one month post-vaccination was >0.5 (2-fold criterion). Results were considered statistically significantly lower, if the upper limit of the 95% CI for the GMT ratio was <1.0.

After concomitant administration, the non-inferiority criterion of HI GMT ratios was met for all influenza subtypes except the influenza A/H3N2 virus: for group 3 compared to group 1, the lower limit of the 95% CI was 0.49, just below the cut-off of >0.5 (2- fold criterion). The non-inferiority criterion for the OI GMT ratio was met for all four pneumococcal serotypes in group 3 compared to group 4. The response against the other 19 pneumococcal serotypes was not determined.

PCV13

Song et al Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine and an MF59-adjuvanted influenza vaccine after concomitant vaccination in ≥60-year-old adults. Vaccine 35 (2017) 313–320

Subjects aged ≥ 60 years were randomized in a 1:1:1 ratio to receive aTIV+ 13-valent pneumococcal conjugate vaccine (PCV13) (Group 1), PCV13 (Group 2), or aTIV (Group 3). HI and OPA assays were used to compare immunogenicity after single or concomitant vaccination. Non inferiority criteria were a lower limit of the 95% CI of the GMT ratios >0.5. In total of 1149 subjects (Group 1, N = 373; Group 2, N = 394; Group 3, N = 382) were available for the assessment of immunogenicity and safety. After concomitant administration, the non-inferiority criteria of GMT ratios were met for all three influenza subtypes and 13 pneumococcal serotypes. Point estimates for the ratios of all three influenza strains were below 1 and the point estimates for the ratios of the pneumococcal serotypes were all except one (serotype 6B) below 1.

Additional expert consultation

As a request from the CHMP, in line with current CHMP guidance, the VWP discussed that inference of superior efficacy for aQIV vs. QIV in children aged 6-36 months based on superior humoral immune responses is not possible. It remains essential that approval of aQIV is founded on a demonstration of superior efficacy vs. a licensed QIV in this age range. It is also necessary to demonstrate that the safety profile of the aQIV is not sufficiently different from that of QIV to cause any concern. On this

matter, the VWP agreed that the safety data for the aQIV would not preclude an approval for use in children aged 6-36 months if there was an adequate demonstration of efficacy.

The VWP noted that most cases of influenza accrued during the pivotal efficacy trial V118_05 were collected in the second season (2014-2015), which was a H3N2 dominated season where the circulating strains were largely unmatched to the vaccine strain. This mismatch would be expected to impact on the efficacy of the aQIV and QIV vaccines. Importantly, the benefit of the adjuvant might however be limited if the antigenic distance between the vaccine strain and circulating strains is beyond the breadth of antibody responses commonly induced by the adjuvanted vaccine. The fact that superiority was not shown for aQIV over QIV in this setting indicates that adding the adjuvant did not result in improved efficacy against poorly matched strains.

The trial failed the primary endpoint.

The trial was not powered for the pre-defined secondary analyses. Nevertheless, among these secondary analyses, the applicant points out: i) statistically superior rVE for the H1N1 matched strains in the 6m-72m age group [59.39%, 95%CI (2.06, 83.16)]; ii) statistically superior rVE in children 6 to <24 months of age [31.37% (3.14, 51.38)]; and iii) early rVE at 7 and 14 days after the first and up to the second vaccination [54.66% (18.08, 74.91) and 70.56% (35.19, 86.62) respectively]. However, some results of secondary analyses are inconsistent by subgroup without biological plausibility for the finding (e.g. superior efficacy for aQIV was shown in male but not female subjects despite the lack of any difference in immune response between sexes).

Since the youngest children are the most likely to be influenza-naïve and therefore might be the group most likely to derive some additional benefit from an adjuvanted vaccine, the VWP particularly noted the rVE in the subset of the 6-24-month-olds, with a lower bound of the 95% CI just above zero (3.14). It was also discussed that there remains an unmet need for influenza vaccines that achieve priming of the influenza-naïve paediatric population since only unadjuvanted vaccines are currently licensed for use in this age range. Nevertheless, the VWP was not persuaded that the data are sufficiently robust to grant a restricted indication in children aged 6-24 months.

2.5.6. Discussion on clinical efficacy (paediatric indication)

The CDC and the WHO recommend the use of two doses (separated by 4 weeks) of inactivated influenza vaccine for subjects 6 months to < 9 years of age who have previously received only 1 dose of influenza vaccine, or who have never received influenza vaccine previously. One dose is recommended for those who have previously received 2 or more total doses of any influenza vaccine. This same approach has been followed in the CTs performed with Fluad Tetra.

The use of half dose of Fluad Tetra (0.25 ml) in younger children (6 to < 36 months) and a full dose (0.5 ml) for older children (36 to 72 months) derives from the dose-finding study V104P2 and the pivotal clinical efficacy trial V118_05. The results from these two studies provided support also for the 2-dose schedule in subjects influenza naïve.

The use of the Hemagglutination Inhibition (HI) assay as the primary assay to assess vaccine immunogenicity in CTs is in line with the recommendations of the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014). However, it should be noted that HI titers are not a true surrogate marker in the sense that there is not an accepted cut-off titer that defines clinical protection.

Comparing HI titers in terms of GMTs and GMRs is considered appropriate. Similarly, the definition of Seroconversion rate (defined as the percentage of subjects achieving either: 1) a prevaccination (baseline) HI titer <1:10 and postvaccination HI titer ≥1:40 after vaccination; or 2) a prevaccination

(baseline) HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer) is also considered appropriate.

For the efficacy assessment, all swab samples from ILI cases were assayed by RT-PCR and sequencing (only for B strains) assays to obtain laboratory confirmation of influenza positive samples, which is considered an adequate approach. These assays were validated and the corresponding reports are considered adequate. Another sample of the swab was used to isolate the influenza virus in cell culture using MDCK cells and/or rhesus monkey kidney cells. To try determining if the infected strains matched or not the vaccine strain, two test were used, a HI and a microneutralization (MN) test specifically designed for identifying antigenic match. The results of the two tests were discrepant, being those obtained with the MN test more in line with the epidemiological data from that season (2014-15), which was known to be a mismatched season for A/H3N2 (i.e., the strain that was circulating in the season was antigenically distinct from the vaccine strain). During assessment of the MAA, it was clear that there was a problem with the serological HI assay used by one of the labs that performed the H3 testing so that many true unmatched H3 strains were erroneously classified as matched strains. When the samples originally tested at this lab were retested at the second lab it was shown that only 5% of H3 influenza cases observed in the CT V118_05 matched the H3 component of the vaccine.

The Clinical Development Plan (CDP) was based on the supportive immunogenicity clinical trials in the paediatric population with an aTIV (Fluad). In addition, the Applicant provides in this MAA data obtained with aQIV, including the results from a dose-finding study (V104P2) and the pivotal trial (V118_05) in which clinical efficacy and immunogenicity was measured using subjects vaccinated with a non-adjuvanted vaccine as the comparator arm.

Since the manufacturing process and formulation of aQIV and Fluad (adjuvanted Trivalent Influenza Vaccine, aTIV) are the same, with the exception of an additional B strain included in aQIV, it is considered that clinical study experience with aTIV in subjects 6 months to <6 years of age provides relevant and valuable data for assessment of the overall immunogenicity and safety of aQIV.

Dose finding study

Overall, study V104P2 was well designed and performed. This trial provided clear support for the use of the MF59 adjuvant in population from 6 to <36 months of age, since all MF59 adjuvanted formulations induced statistically superior antibody responses compared to a nonadjuvanted vaccine against both homologous vaccine A strains in terms of GMTs.

The second vaccination with the MF-59 adjuvanted formulations increased the GMT titers obtained after the first vaccination, which gives support for the 2-dose schedule in influenza vaccine naïve subjects.

In conclusion, results from trial V104P2 provides clear support for the using the MF59 adjuvant, and a 2-dose-schedule.

Pivotal clinical study

Overall, the study design (V118_05) was in agreement with a CHMP Scientific advice and it was considered adequate. Importantly, as stated in the current CHMP guideline on influenza vaccines, clinical efficacy for children 6 to 36 months of age was to be demonstrated against laboratory confirmed influenza disease.

The study (V118_05) was a randomised, active controlled observer blind study. Due to difference in appearance of the study vaccines, as well as the unavailability of a 0.25 mL pre-filled syringe formulation for aQIV in Study V118_05, this study was conducted under observer-blind conditions. The fact that the pivotal trial was not a double-blinded trial is acceptable.

The inclusion and exclusion criteria are considered adequate. In fact, most of the subjects enrolled in the trial were healthy children. Subjects being at high risk of complications from influenza (like subjects with asthma, chronic lung disease, heart disease, kidney or liver disorders, etc.) were not excluded in this CT. This approach is considered adequate since across European Union Countries there is a general recommendation for vaccinating this risk group.

The vaccine strain composition for the aQIV was unchanged between Seasons 1 and 2, and contained the strain composition recommended for the Northern Hemisphere.

For Season 1, aQIV was compared to TIV-1, and for Season 2, QIV-1 was used as a comparator. The use of a trivalent comparator at the time of study initiation was due to the fact that the QIV-1 comparator was only recently licensed for use in the US and not available in sufficient quantities.

A majority (85%) of the subjects were enrolled during Season 2 and the majority of influenza cases came from Season 2. Therefore, the inclusion of TIV-1 as the comparator in Season 1 of study V118_05 is not considered to have an impact on the overall study outcome.

Enrolled subjects were randomly assigned to one of 2 study groups (aQIV or non-adjuvanted comparator) in ratio of 1:1 with stratification factors as study site, age group (≥6 to <36 months of age/ ≥36 to <72 months of age, ratio 1:1), vaccine status (naïve/ non-naïve) and for presence of high risk medical condition (at risk/not at risk). This approach is considered adequate to eliminate biases that could result from these parameters, particularly form the age and the vaccine status.

The definition of the different populations for the assessment of the clinical efficacy and immunogenicity are considered appropriate. The immunogenicity subset was to contain all subjects enrolled in season 1 and from the first 4,000 subjects enrolled in season 2 a subset of 1,780 subjects would be included.

The primary measure of efficacy was the estimate of rVE of aQIV relative to non-adjuvanted comparator for preventing first-occurrence RT-PCR-confirmed influenza disease caused by influenza strains related to those contained in aQIV and non-adjuvanted comparator in children ≥6 to <72 months of age, for ILI cases occurring at ≥21 days and ≤ 180 days after the last vaccination or until the end of the influenza season, whichever was longer. This as well as the ILI definition applied can be considered appropriate since the primary endpoint is clinically relevant.

During the procedure, the Applicant presented then data showing the relative vaccine efficacy by age subgroup (≥6 to <12 months, ≥12 to <24 months, and ≥24 to <36 months). The rVE of aQIV is similar in subjects 6 to <12 months and ≥12 to <24 months of age (35.76% and 28.83%, respectively). CHMP concluded that from the data provided it was however clear that none of these rVE estimates were statistically significant. Most of the influenza cases in the age group ≥6 to <24 months were due to H3 strains, which were unmatched to the vaccine H3 component.

All swab samples from ILI cases were also cultured for the growth of the clinical strain of influenza obtained from these subjects, to allow for antigenic characterization. i.e., determining whether the clinical isolate is antigenically matched or antigenically unmatched to the vaccine strain. This information was then used to calculate vaccine efficacy according to the antigenic match to the vaccine strain. This approach is considered appropriate.

From a statistical perspective, the interpretation of the analyses on the efficacy secondary objectives is not considered adequate (see further discussion below). Due to the numerous analyses with the same level of alpha (5%) is highly probable that it has caused a multiplicity problem.

Overall, the immunogenicity endpoints are considered adequate and are in line with the requirements of section 6.1.2 of the current CHMP guideline on influenza vaccines (EMA/CHMP/VWP/457259/2014). The immunogenicity objectives aimed at showing non-inferiority/ superiority of HI antibody responses

of aQIV vs TIV/QIV against each of the influenza strains are relevant to assess the effect of the MF-59 adjuvant and to help understanding the clinical efficacy data. These analyses were performed measuring the effect in terms of GMTs and SC rates, which are considered relevant parameters.

The statistical methods to assess immunogenicity objectives are considered adequate. The non-inferiority and superiority margins used for ratio of GMTs and differences in SC rates are commonly used in influenza vaccines, and are described in the CBER guideline "guidance on Seasonal Influenza Vaccines May 2007)". These margins are considered adequate.

One of the secondary objectives is the evaluation of the antibody response according to the Center for Biologics Evaluation, Research, and Review (CBER) criteria (2007). This analysis is considered informative but not critical for the immunogenicity assessment of the vaccine.

The secondary objectives related to Healthcare Utilization and Health Economic Outcomes, are not considered critical for the risk/benefit analysis of this vaccine.

No relevant amendments were made to the original protocol.

Conduct of the study

Practically all subjects enrolled were exposed to the vaccine. Approximately 15% of the exposed subjects did not complete the protocol. Although this figure is relatively high, it was similar in both arms. Moreover, the reasons for discontinuation were similar in the aQIV and the comparator group, being the most important lost to follow-up [around 4.6%] subjects) and enrollment in the V118_05E1 study (4.3%] subjects). Analyses of these data did not show any indication of selective discontinuation for safety reasons.

The study was conducted in 9 countries, including several European countries, being most of the subjects recruited in USA. Subjects from tropical countries were also recruited. As detailed below, no difference by race and ethnicity was observed upon subgroup analysis. It is thus considered that the data obtained from this population can be extrapolated to the EU population

All baseline characteristics in efficacy and immunogenicity sets well balanced between the two arms. A similar conclusion was reached when baseline characteristics were analysed according to other parameters such as baseline HI titer, age, naivety, risk, gender and by season. Of interest, 8.7% of enrolled subjects were considered at high risk of influenza complication.

A substantial proportion of vaccine naïve subjects had antibody HI titres ≥1:10 and 1:40 at baseline (variable for strains), reflecting that this is not an influenza naïve group but a vaccine naïve group. Within the responses to D120 LoQ, the Applicant submitted these data by age group (6-24 m, 24-36 m, 36-72 m).

Clinical efficacy Results

The primary endpoint aimed at demonstrating a difference in rVE between aQIV and the comparator vaccine group was not met in subjects ≥6 to <72 months of age in the FAS, since the pre-specified statistical criterion (LL of the 2-sided 95% CI for the rVE >0%) of the rVE estimate was <0 (rVE -0.67 [95% CI: -19.81; 15.41]). A similar result was obtained in the PPS. It is considered that this result precludes granting a marketing authorization for subjects ≥6 to <72 months of age.

The Company has performed secondary efficacy analyses that include a large number of comparisons assessing rVE in a number of subgroups.

Before discussing on these secondary efficacy analysis it is important to mention that most of the influenza cases detected in the trial (396 of the 508) (78%) were caused by an H3 virus and that 95% of these H3 cases were due to strains antigenically unmatched to the H3 vaccine component of the

vaccine. In fact, from 56% of RT-PCR confirmed influenza cases it was possible to isolate the virus in cell culture and then analyse whether the virus was antigenically matched or unmatched to the viral antigens present in the vaccine. As shown above (in section Relative Vaccine Efficacy: Culture-Confirmed Influenza), the original MAA included two different analyses and it is clear now that there was a problem with the serological assay used by one of the labs that performed the testing so that many true unmatched H3 strains were erroneously classified as matched strains. Thus, the data that reflect the situation of trial V118_05 are those described in the previous section, which indicates that only 5% of H3 influenza cases observed in the CT V118_05 matched the H3 component of the vaccine.

The CT V118_05 was conducted during two seasons (2013/2014 NH and 2014/2015 NH, with over 85% of the subjects enrolled during the second season) and that 98% influenza cases were reported during the second 2014/2015 NH influenza season. The observation that most of H3 cases in trial V118_05 were antigenically different from the vaccine component was in agreement with the epidemiological data gathered from that season.

It is important to note that due to major mismatch for the predominant A/H3N2 strain, all 2014/2015 influenza vaccines exhibited especially low effectiveness in all age groups, including children <6 years of age (CDC 2019). Moreover, Zimmerman et al (Clinical Infectious diseases 2016: 6-63) showed that in season 2014/15, influenza vaccines offered little protection against the predominant influenza H3N2 virus since in the USA the adjusted vaccine efficacy against H3-associated illness was 6% (95CI, -5% to 17%). As discussed below, most likely, both vaccines in trial V118_05 showed the same lack of efficacy.

All these issues have important implications regarding the usefulness of trial V118_05 to assess the rVE of Fluad Tetra vs the non-adjuvanted comparator.

The secondary efficacy comparisons made were:

1) For the age group ≥6 to <72 months of age:

- According to RT-PCR-Confirmed Influenza by strain
- According to Culture-Confirmed Influenza by strain.
- According to Prior Vaccination Status (two analyses: RT-PCR- and cell culture Confirmed influenza cases)
- According to Risk status (two analyses: RT-PCR- and cell culture -Confirmed cases)
- According to season (two analyses: RT-PCR- and cell culture Confirmed cases).

2) In different age groups. The four age subgroups chosen were: ≥6 to <36 months, ≥36 to <72 months age group; ≥6 to <24 months and ≥24 to <72 months. For each group, rVE was calculated:

- According to RT-PCR -Confirmed Influenza
- According to cell-culture confirmed influenza (all, matched and unmatched strains)

3) Additional secondary analyses were performed according to what the Company consider to be "early efficacy", i.e.

- assessing rVE in vaccine naïve subjects for two periods of time: ≥7 and ≥14 days after first and up to second vaccination. It is important to mention that the second vaccination was given at day 28. So in fact, rVE is being measured for a very short period of time, for only 14 or 21 days.
- assessing rVE in all subjects for two periods of time: ≥7 and <21 days after last vaccination and for ≥7 and <180 days.

For the analyses performed with cell culture confirmed cases, additional calculations of rVE were made depending on whether the isolated viral strains were matched or not to the vaccine strains. Moreover, for all of the analyses indicated above, calculation of rVE was made in relation to cases caused by "any influenza strain" and by each of the four individual viral components (H1, H3 and the two B strains). Thus, in total more than 200 secondary calculations of rVE were made. All these rVE calculations used the same alpha (5%) error.

Assessment of these secondary analyses would have been very relevant in case the primary efficacy objective had been met. In that case, the secondary analyses could have provided clues on the particular subgroups or factors that were responsible for the better efficacy of the aQIV vs the non-adjuvanted comparator. However, since the primary efficacy endpoint was not met, it is complicated to infer any solid conclusion to support granting a marketing authorization from these secondary efficacy analyses. In fact, according to the Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) "the use of a subgroup to rescue a trial that has formally failed…from a formal statistical point of view, no further confirmatory conclusions are possible in a clinical trial where the primary null hypothesis cannot be rejected", accordingly, from a regulatory perspective, the post hoc analyses proposed by the Applicant are not valid to rescue the trial. Once the superiority for the primary objective is not met, there is no possibility to spend alpha in any subgroup analysis.

Based on the RT-PCR confirmed cases, it was observed that most of the cases were due to H3N2 viruses (396 cases out of 515). No difference in rVE between aQIV and comparator was demonstrated for the RT-PCR-confirmed A/H3N2 and B strains in subjects ≥6 to <72 months of age, and only a marginally better rVE than comparator vaccine was seen against the RT-PCR-confirmed A/H1N1 strains; rVE: 59.39 (95% CI: 2.06; 83.16).

395 out of the 396 H3 cases occurred in the second season, in which the circulating strain was antigenically different from that of the vaccine. As discussed below, data from the trial showed that rVE for H3 unmatched strains was not statistically significant [3.14 (95%CI: -30.61; 28.17)], which most likely is a consequence of none of the two vaccines being efficacious against this H3 antigenic variant. So, of the 395 H3 cases in season 2 (and according to the serological characterization of cases), it is expected that 95% of them (375 cases) were unmatched to the vaccine. As indicated above, no clinical protection against H3 cases it is expected to be provided by the vaccine, and thus if these H3 cases were excluded from the primary objective analyses, the total number of cases observed in the trial would be 133 cases (508 minus 375). It is important to highlight that this figure is much lower than the minimum number of 323 cases that was needed (according to the clinical statistical plan: sample size and Power Considerations of Primary Objectives in section 9.7.2 of the CSR) to be able to evaluate the primary objective. In fact, the Company states: "In the situation when the dominant circulating influenza strains have a major antigenic difference with the vaccine strain, resulting in a low vaccine efficacy, it is not possible to demonstrate a statistically significant difference in clinical efficacy between adjuvanted influenza vaccine and comparator and meet the prespecified success criteria for the primary endpoint."

Thus, in conclusion, and in agreement with the Applicant, the fact that most of the influenza cases observed during the trial were due to an H3 variant antigenically different from the vaccine component makes it "not possible to demonstrate a statistically significant difference in clinical efficacy between adjuvanted influenza vaccine and comparator". Thus, it is considered that the data from the trial are inconclusive and thus they cannot serve as a support for granting a paediatric indication.

Immunogenicity Results

In terms of immunogenicity, aQIV elicited a robust postvaccination immunogenic response against all 4 strains contained in the vaccine which met CBER's immunogenicity criteria. Moreover aQIV elicited a superior immunogenic response (as reflected by GMT ratio [GMTaQIV/GMTcomparator]), having a

lower 95% CI limit >1 and SC difference with a lower 95% CI limit >0 for all homologous strains tested relative to the comparator vaccine for all prespecified age groups. In fact, the LL of the 2-sided 95% CI of the GMTr exceeded 1.5 for all homologous strains.

In relation to the heterologous immune response, it has been shown that the GMTs for heterologous A/H3N2 and the B heterologous strains were higher in aQIV group than in the comparator vaccine group at 21 days after the last vaccination. These results do not appear to have any clinical relevance in terms of protection of clinical disease since rVE was not superior for unmatched strains.

A number of subgroup analyses was also performed regarding age, dose, vaccine naivety, baseline serological naivety, risk status, sex, and race. The subgroup analyses immunogenicity results focus on a comparison of GMTs and SCRs. Overall, in all comparisons the aQIV group had higher GMT values, SCRs, and percentages of subjects with HI titer ≥1:40 than the comparator group after the first (non-naïve) and second vaccinations (naïve).

The GMTr was higher in the ≥6 to <36 months age group (ranging from 2.08 to 2.58) than in the ≥36 to <72 months age group (ranging from 1.33 to 1.94) for all homologous strains at 21 days after last vaccination. The GMTr was higher in the ≥6 to <24 months age group (ranging from 2.48 for the homologous A/H3N2 to 3.72 for homologous B/Victoria) than in the 24 to <72 months age group (ranging from 1.47 for homologous A/H3N2 to 1.77 for homologous B/Yamagata) at 21 days after last vaccination. This suggests a potential greater benefit of the adjuvant in younger children. Similarly, greater GMT ratios were seen in vaccine naïve subjects as compared to vaccine non-naïve subjects, as well as in subjects who had pre-vaccination titres <1:40 as compared to those with pre-vaccination titres ≥1:40. This could suggest that aQIV induces a better priming response as compared to non-adjuvanted influenza vaccines, which would be in line with the purported advantages of the MF59 adjuvant.

In relation to the dose used, aQIV elicited a superior immunogenic response for all homologous strains tested relative to the comparator vaccine for both groups of 0.25 mL dose and 0.5 mL dose.

Data on long-term persistence of the antibodies showed that the greater immunogenicity of aQIV relative to the comparator vaccine in subjects 6 to <72 months of age was also evident at 180 days after the last vaccination in Study V118_05.

In addition to HI responses, the immune response was also determined with a microneutralisation (MN) assay and were reported for the A/H3N2 strain and B/Yamagata strain, with superior responses in the aQIV group compared. The MN results for the A/H3N2 strain and the B/Yamagata strain appear to follow the same patters as the HI results.

Immune response upon revaccination

Two studies measured the immune response after revaccination (V118_05E1 and V118_05E3). Subjects recruited for these studies were a subset of those included in the pivotal trial V118_05. After Season 1 of trial V118_05, some subjects were invited to enroll in revaccination study V118_05E1. Similarly, after Season 2, some subjects were invited to enroll in revaccination study V118_05E3.

In study V118_05E1 subjects received the same influenza vaccine and the same strains as administered in the pivotal study, i.e., aQIV or licensed nonadjuvanted comparator influenza vaccine. In study V118_05E3 subjects were re-randomized to receive the same or different quadrivalent vaccine type (adjuvanted or nonadjuvanted) from what they had received in Study V118_05, which resulted in 4 treatment groups (aQIV/aQIV; aQIV/QIV-1; QIV-1/aQIV; QIV-1/QIV-1).

The immune response was measured by three assays: HI, microneutralization (MN) and anti-Neuraminidase antibodies. Overall, the results from the three assays were in the same line and showed that:

- Baseline titers were generally higher for subjects that received aQIV than the non adjuvanted comparator. This has already been described above in this assessment report in section "persistence of immune response"
- In general, there were similar antibody titers in the aQIV/aQIV, aQIV/QIV-1, and QIV-1/aQIV groups and these titers were higher compared with the repeated nonadjuvanted group. It is mentioned that this conclusion was observed in most cases, but there were some exceptions depending on the strains and the assay used.

In conclusion, the results from these studies showed an adequate immune response following the revaccination of subjects that received aQIV, both when revaccinated with aQIV or with a non adjuvanted vaccine.

The results show that although the GMTs and GMRs are higher for all strains when vaccinated with aQIV two years in a row as compared to being vaccinated with aQIV and subsequently with QIV, the differences is not substantial. As such, immunological benefits of annual revaccination with aQIV is not firmly established within study V118_05E3.

It is agreed with the Applicant that altogether, the supportive studies with aTIV showed that vaccination with aTIV produces a robust immune response (in terms of GMTs, and SCRs) which is higher compared to nonadjuvanted influenza vaccines. These results provide additional support for the role of MF59 as an adjuvant. Importantly, the results are broadly in line with the immunogenicity data obtained with the aQIV.

2.5.7. Conclusions on the clinical efficacy (paediatric indication)

Overall, the study design of the pivotal efficacy trial V118_05 was in agreement with a CHMP Scientific advice and it was considered adequate.

In terms of immunogenicity, it is shown that aQIV elicited a superior immunogenic response (as reflected by GMT ratio [GMTaQIV/GMTcomparator]), having a lower 95% CI limit >1 and SC difference with a lower 95% CI limit >0 for all homologous strains tested relative to the comparator vaccine for all prespecified age groups.

Nonetheless, this superior immunogenicity of aQIV does not translate into a better vaccine efficacy since the primary endpoint aimed at demonstrating a difference in rVE between aQIV and the comparator vaccine group was not met in subjects ≥6 to <72 months of age in the FAS, since the pre-specified statistical criterion (LL of the 2-sided 95% CI for the rVE >0%) of the rVE estimate was <0 (rVE -0.67 [95% CI: -19.81; 15.41]). A similar result was obtained in the PPS.

Since the primary efficacy endpoint was not met, it is complicated to infer any solid conclusion to support granting a marketing authorization from these secondary efficacy analyses. In fact, according to the Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) "the use of a subgroup to rescue a trial that has formally failed…from a formal statistical point of view, no further confirmatory conclusions are possible in a clinical trial where the primary null hypothesis cannot be rejected", accordingly, from a regulatory perspective, the secondary analyses proposed by the Applicant are not acceptable.

It is considered that this result precludes granting a marketing authorization for the paediatric subjects ≥6 to <72 months of age.

The Applicant withdrew the paediatric indication during the procedure.

2.5.8. Discussion on clinical efficacy (elderly population)

Adjuvanted Quadrivalent Influenza Vaccine (aQIV) is a seasonal, surface antigen, inactivated influenza vaccine, adjuvanted with MF59C.1 (MF59). The manufacturing process, dose and formulation of aQIV and Fluad (EU authorized adjuvanted Trivalent Influenza Vaccine, aTIV) are the same, with the exception of an additional B strain included in aQIV. aTIV is authorised in many EU countries since 1997 and it is indicated for subjects >65 years of age.

This vaccine contains the influenza hemagglutinin (HA) antigen from four egg-grown viral strains, and the adjuvant MF-59. The dose of 15 µg HA (in 0.5 ml) per viral strain (in 0.5 mL) is in agreement with the Eur. Ph. requirements and is also the one used in all approved trivalent or quadrivalent inactivated influenza vaccines marketed in the EU. Thus, this dosage of HA is considered adequate.

It is also considered adequate that the selection of influenza viral strains in each formulation of aQIV and aTIV has been/will be done following the WHO annual (seasonal) recommendations.

Vaccine Dose and Schedule

The vaccine dose and dosing schedule of aQIV and aTIV are considered appropriate. They are based on those of licensed influenza vaccines and pertinent data from ranging dose clinical studies V104P3 and V7P38.

Assays supporting immunogenicity assessment

Overall the assays performed to support the Immunogenicity assessment are considered adequate. During assessment several topics were additionally justified.

The use of the Hemagglutination Inhibition (HI) assay as the primary assay to assess vaccine immunogenicity of the vaccine in CTs is in line with the recommendations of the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014). However, it should be noted that even when several studies of influenza infection have indicated that HI antibody titres of 1:40 or greater are associated with protection from influenza illness, HI titers are not a true surrogate marker in the sense that there is not an accepted cut-off titer that defines clinical protection. The validation report provided in relation to the HI test performed by the different labs is considered adequate. The applicant compares HI titers in terms of GMTs and that is agreeable. Similarly, the definition of Seroconversion rate (defined as the percentage of subjects achieving either: 1) a prevaccination (baseline) HI titer <1:10 and postvaccination HI titer ≥1:40 after vaccination; or 2) a prevaccination (baseline) HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer) is also considered appropriate.

The burden of influenza disproportionately falls on individuals <5 years of age and ≥65 years of age. The higher burden of influenza among older adults relative to younger adults is in part related to the age-related decline of the immune response (immunosenescence), which increases their susceptibility to influenza and risk of serious complications, leading to increased influenza related hospitalizations and deaths. Influenza also contributes substantially to the mortality rate among ≥65 years of age.

The clinical development program of Fluad Tetra to support the indication for subjects ≥ 65 years of age is based on the assumption that aQIV, which is manufactured and formulated in the same way as aTIV (Fluad) with the exception of the additional B strain included in aQIV, is safe and will lead to protection against influenza disease as demonstrated previously for aTIV, with the additional benefit of protection against both B strains. It should be noted that Fluad was approved in Italy in 1997 and subsequently in other EU countries, US and Australia and that more than 102 million doses have been distributed worldwide, mostly for use in older adults.

According to the CHMP Guideline on Influenza Vaccines (Non-clinical and Clinical Module), the main requirement for a (new) adjuvanted surface antigen vaccine in the elderly is to demonstrate an

advantage in terms of immune responses, which may be based on superior immunogenicity vs a non-adjuvanted but otherwise comparable authorised vaccine.

An advantage for the adjuvanted vs. non-adjuvanted formulation could include a higher seroconversion rate, higher antibody titres (based on GMTs or proportions reaching a predefined cut-off titre) or other immune response parameters, including increased breadth or duration of response.

Design and conduct of clinical studies

The clinical development plan (CDP) for Fluad Tetra to support the indication for subjects ≥ 65 years, is found acceptable and it is based on a pivotal trial with aQIV (V118_20), which evaluated that the second B strain elicited an antibody response and that it did not interfere in the immunogenicity elicited by the other three strains. Additionally, there is another pivotal study (V70_27) aimed at demonstrating the advantage of the inclusion of the adjuvant, comparing aTIV versus TIV. Additionally, a supportive absolute efficacy study (V118_18) and several supportive studies with aTIV. Also, two effectiveness studies are presented carried out with aTIV.

Dose-finding studies

These studies were all performed with aTIV. The two dose-ranging studies V104P3 and V7P38 evaluated the effect of various antigen and MF59 dose levels on immune response to aTIV using a validated HI assay. Overall studies V104P3 and V7P38 are considered well designed and performed. These trials provided clear support for the use of the proposed HA dose and MF59 adjuvant in elderly population, since all MF59 adjuvanted formulations induced statistically superior antibody responses compared to a nonadjuvanted vaccine.

Pivotal study V70_27

Study V70_27 is a randomized observer-blind, controlled multicentre study conducted in the 2010/2011 season in the USA, Philippines, Colombia, and Panama. The immunogenicity of aTIV was compared to TIV in terms of the HI response against homologous strains (vaccine strains) and against heterologous strains to determine breadth of immune response. Persistence (duration) was also measured 6 and 12 months after vaccination.

In study (V70_27), the first (lot-to-lot consistency) and third (noninferiority according to CHMP criteria) co-primary objectives were met. Regarding the second co-primary objective, noninferiority of aTIV relative to TIV was demonstrated against the 3 homologous influenza strains according to CBER criteria, but superiority of aTIV to TIV for at least 2 homologous strains was not demonstrated. In a posthoc analysis, it was shown that aTIV elicited significantly higher GMT levels and SCR than TIV against all 3 homologous strains, demonstrating the benefit of the MF-59 adjuvant in subjects ≥65 years of age.

The design of the study is considered appropriate. The HI response was expressed as GMT ratio's (aTIV/TIV) and SCR differences (aTIV-TIV) at day 22, three weeks after vaccination. Persistence (duration) was also measured 6 and 12 months after vaccination (D181, 366). These endpoints are considered relevant and are agreed for the determining whether there is an immunological advantage of the adjuvant. Effectiveness, i.e. the relative rate of influenza like illness between the two groups, was also determined however no laboratory confirmation of ILI cases was performed therefore these analyses are of limited value. The protocol prespecified that superiority could be concluded if the LL of the 95% CI around the GMTratio (aTIV/TIV) was >1.5 and the LL of the 95% CI around the SCR difference was >10%. Note superiority margins were 1 and 0% for GMT ratio's and SCR difference in study V118_20.

Overall, responses are relatively consistent between the different age cohorts, keeping in mind the relatively wide CIs in particular in the oldest age group due to a small number of subjects.

Randomisation was stratified by age with 65 to 74 years versus ≥75 years, and this is considered acceptable.

The 7 supportive studies that compare immune response following aTIV versus TIV vaccination show a generally higher antibody response with the adjuvanted vaccine. Therefore, all these data are in the same line than those observed in the pivotal aQIV study V118_20 and both sets of data show that the adjuvanted vaccine is more immunogenic than the non-adjuvanted comparator.

The approval of the aTIV was based on its better immunogenicity as compared to a non-adjuvanted vaccine, taking into account that the slightly higher reactogenicity of aTIV compared to TIV did not significantly alter the B/R of aTIV compared to TIV. The better protection of adjuvanted vaccines versus non-adjuvanted vaccines is inferred by the higher antibody response that they trigger, but as commented before there is no true immunological marker that correlates with protection against the influenza disease. It should be kept in mind that there is no demonstration that immunogenicity is a valid surrogate measure for efficacy.

Pivotal study (V70_27) evaluated antibody persistence at 6 and 12 months after vaccination, in homologous and heterologous strains. In all tested strains, only A/H3N2 demonstrated a statistically significant difference in GMT ratio comparing aTIV with TIV at 6 and 12 months. No strong conclusion can be made of a better persistence of antibodies for the adjuvanted vaccine as compared to that of the non-adjuvanted vaccine.

Regarding the revaccination studies, in general the results show that the immunogenicity elicited by the successive administration of the aTIV is in many cases higher than with the TIV, but in any case always non-inferior. These are adequate results for a vaccine that is intended to be administered annually to its target population.

Pivotal study V118_20

Pivotal aQIV study V118_20 was a phase 3, randomized, double-blind, comparator-controlled, parallel-group, multicentre study conducted in 2017/2018, in which the immunogenicity of aQIV is compared to two aTIVs (aTIV-1, aTIV-2), each containing one of the two B strains contained in aQIV. The main objective was to demonstrate non-inferiority of the immune response to aQIV to that of aTIV-1, containing the B-Vic strain, and aTIV-2, containing the B Yam strain based upon the GMT ratio and SCR.

The design of study V118_20 is found appropriate as it is in line with the CHMP Guideline on influenza vaccines, Non-clinical and Clinical module.

As stated by the Applicant, study V118_20 enrolled 1778 subjects in total, 771 (43.4%) male and 1007 (56.6%) female ≥65 years old. Although there is an imbalance in the gender of the enrolled participants, the applicant has justified that this is consistent with the population demographics in the US, where the study was carried out.

Most common medical conditions are well balanced between the study arms. In study V118_20 high-risk subjects had 1 or more of the following predefined comorbidities, with no substantive differences between vaccine groups: congestive heart failure (6%), chronic obstructive pulmonary disease (COPD; 13% to 14%), asthma (12%), hepatic diseases (<1% to 1%), renal insufficiency (4% to 5%), and the most commonly reported neurological/neuromuscular or metabolic conditions including diabetes mellitus (82% to 83%).

The applicant stratified the response by sex (male, female), and by previous vaccination history and found no notable differences between the aQIV group and the aTIV groups. For subjects without vaccination history seroconversion rates appear to be higher for all four strains for the aQIV as well as the aTIV groups. The applicant has also analysed the data for subjects with pre-existing comorbidities at risk of severe influenza versus subjects without pre-existing comorbidities at risk of complications after influenza, and these seem to respond in a similar way to the vaccine.

Apart from the issues that have been mentioned above, the study inclusion and exclusion criteria are considered adequate.

Study V118_20 was conducted entirely in the US and during one influenza season (2017-2018). Study participants received one single vaccination. One of the two vaccines used as comparators in the study (aTIV-1) was a commercial vaccine (Fluad) and the other one (aTIV-2) was only formulated for the V118_20 study, since it contained the alternate B strain that was contained in the aQIV vaccine but not present in Fluad. The three vaccines used as treatment in this study are acceptable.

The co-primary objectives, to demonstrate non-inferiority of aQIV in comparison to the aTIV vaccines with the two alternate B strains and to assess the immunogenicity in accordance to the CBER criteria, are considered adequate. Nevertheless, it should be kept in mind that the CBER criteria are presented in order to comply with FDA requirements, but do not apply to the EU requirements.

Regarding the secondary immunogenicity objectives, to characterize the immunogenicity of aQIV, aTIV-1 and aTIV-2 and to demonstrate superiority of aQIV for the B strain that is not included in the corresponding aTIV, are also found to be acceptable.

The co-primary and secondary endpoints are clearly defined and have clinical relevance. The immunogenicity and safety endpoints are adequate and are in line with the requirements of the current CHMP guideline on influenza vaccines (EMA/CHMP/VWP/457259/2014) and in line with the Center for Biologics Evaluation, Research and Review (CBER) criteria (2007).

The randomization was carried out without any stratification by age, comorbidities or any other criteria, although an analysis of the results is carried out taking these subgroups into account. The CHMP guideline on influenza vaccines (EMA/CHMP/VWP/457259/2014) recommends that the elderly population is stratified by age, and highlights that every effort should be made to enroll a representative sample of subjects above 75 years of age and to stratify according to age. It would have been optimal to randomize taking the age of the subjects into consideration, in order to have a representative number of subjects from each age subgroup (65-74, 75-84 and ≥85 years of age). The Applicant explains the imbalance between the age strata for subjects enrolled in study V118_20 by showing that this imbalance reflects the US population demographics for the 65-74 and the 75-84 age groups. This is not the case in the ≥85 age group, in which the proportion of the V118_20 study population is much smaller than in the US resident population. This discrepancy is explained by the great number of medical conditions in this group that lead to the exclusion from the enrollment for the study.

Regarding the sets defined for the study analyses, the five populations were well defined and are found acceptable. Also, the subgroups that will be analyzed and the statistical methods to assess the immunogenicity objectives are adequate for the type of vaccine and kind of population.

Practically all subjects enrolled were exposed to the vaccine. Only 1-2% of the exposed subjects did not complete the study protocol. The reasons for discontinuation are similar in the three arms. There are no notable differences in the proportion of subjects excluded from the PPS Immunogenicity between all groups.

Taking into consideration the particularities of influenza vaccines (their seasonal variability, the fact that the vaccine strain does not always match with the circulating viruses, etc.) to conduct the study in only one season is considered adequate. Additionally, it is considered that the race and ethnicity of the US population that has participated in the study can be extrapolated to the EU population. Therefore, the recruitment of the study is acceptable.

Regarding the subject distribution, the imbalance in the gender has been explained as it reflects US demographics for that age group. The rest of the demographic and baseline characteristics are either well balanced or easily explained.

Regarding the medical history and concomitant medication, having in mind the advanced age of the subjects in this study and that the study participants included subjects with comorbidities that increased their risk of complications from influenza infection, it is expected that many (97.7%) of the participants had at least one disorder in medical history. Concomitant medications have been recorded in the Concomitant Medication case report form (CRF), and in case it would be necessary, this information could be used to interpret a possible effect in the clinical study results. The percentages of subjects taking one or more concomitant medications were similar (aQIV, 93.6%; aTIV-1, 92.1%, aTIV-2, 94.8%. Additionally, the proportions of each of the medications taken by >5% of subjects across vaccine groups were, in general, relatively similar.

In study V118_20, the first co-primary objective (to demonstrate non-inferiority of aQIV as compared to aTIV-1 and aTIV-2 in terms of GMT ratios and differences in SC rates), was met for all four strains. The second co-primary objective (to demonstrate adequate immunogenicity according to CBER criteria) was met for the two A strains but not for the two B strains). The fact that the CBER criteria are not met for the B strains does not preclude granting a marketing authorization, since the current CHMP guideline for the clinical assessment of influenza vaccines to be used in the EU does not require these criteria to be achieved. Moreover, it is noted that the previous CHMP criteria required for annual update of influenza vaccines were similar to those from CBER, and it was common to have the same situation described here, i.e., not all three criteria were met. In fact, for annual update, it was required to meet only one of the three criteria.

All of the secondary objectives were met, both in the PPS population and in the FAS population. Importantly, immunologic superiority of aQIV relative to aTIV for the alternate B strain was met. Consistently in all of the secondary outcomes, the obtained results tended to be higher for the A strains (A-H3N2 and A-H1N1) than for the B strains, but always inside the margins established for success.

It should be noted that the immunogenicity was only measured for the homologous strains. Immune response against heterologous strains has not been assessed in this study. As mentioned above, the applicant has stated that response against heterologous strains was not assessed in study V118_20 for aQIV because in their opinion sufficient data from aTIV studies was already available. Regarding the subgroup analyses, they were carried out, by age, gender, race, comorbidity, and vaccination history for each influenza vaccine strain for percentages of subjects with HI titer ≥1:40, GMTs, GMRs, and seroconversion rates. Overall, there were no significant differences in the obtained results in this subgroup assessment.

Nevertheless, some differences in the immune response were observed when subjects were stratified by age (age subgroups 65-74, 75-84 and ≥85 years), with an inferior lower immune response in the more elderly group (≥ 85 years), which can be explained by the immunosenescence that affects subjects more as they are older. Another difference that can be underlined is the one observed between subgroups with a different comorbidity risk score. Those subjects with a high risk of complications after an influenza infection had a lower immune response than those at low risk of complications. This could be an expected result if the high-risk factor was in some way correlated with

a weaker immune system, but this is unknown. The differences are not very large. And finally, in the subgroups made by vaccination history, the results show that subjects that have not been vaccinated against influenza in the last 5 years tended to have a higher GMR and SCR than subjects with a recent history of vaccination. This is a common situation observed for influenza vaccines and relates to the fact that the baseline of those previously vaccinated tends to be higher than those not vaccinated previously and thus the ratio of titres (in terms of GMT and SC rates) pre and post vaccination tend to be higher in those not previously vaccinated.

All the observed results by subgroup analysis are found acceptable and respond to the particularities of the subjects enrolled in this study, which is a population with an age and comorbidities that have a strong influence in the immune response.

Supportive study V118_18

The applicant has submitted the Clinical Study Report of a Phase 3 absolute efficacy study (V118_18) to evaluate the efficacy, safety and immunogenicity of aQIV compared to a non-influenza vaccine comparator in subjects ≥65 years of age.

The results of study V118_18 were not submitted at the time of initiating this MAA since they were not available at that time. In response to the D120 LoQ, the Applicant submitted the CSR for this study.

The goal of this study was to demonstrate that Fluad Tetra prevents influenza in elderly adults. Direct comparison with a non-influenza comparator vaccine (Boostrix) licensed for use in elderly adults, enabled an estimation of the absolute efficacy of aQIV in preventing influenza in elderly adults.

The design of study V118_18 was discussed in a previous CHMP Scientific Advice (EMA/CHMP/SAWP/404125/2016). As indicated in the CHMP report to this SA, the overall design of the study was considered acceptable. As it was indicated in the report, the trial should be conducted in regions in which vaccination of the elderly is not part of the routine immunization program. The Applicant has conducted the study in countries that either do not have a national recommendation regarding seasonal influenza vaccination in elderly patients or where the rates of vaccination are reported to be significantly below 50%. This is accepted.

Participants in the study were males and females ≥65 years old who were healthy or had co-morbidities.

The primary and secondary efficacy objectives aimed at demonstrating absolute VE of Fluad Tetra vs a non-influenza comparator (based on RT-PCR or cell-culture confirmed cases) are clearly defined and have clinical relevance. The efficacy endpoints were analysed using two ILI definitions for influenza (protocol-defined ILI and modified CDC ILI definition), but the protocol-definition of ILI was used to determine success for the primary and secondary efficacy endpoints. This ILI definition was wider and as shown below captured milder influenza disease. It was also considered adequate that there was a secondary objective to characterize the immunogenicity of Fluad Tetra measured according to HI titers.

The primary efficacy and key secondary efficacy objectives were considered achieved if the lower limit (LL) of the adjusted two-sided 95% CI of absolute VE exceeded 40%. This success criterion is considered adequate.

It was planned to randomize 10,692 subjects, 5,346 per vaccine group (Fluad Tetra or Boostrix) but the final number of enrolled subjects were 6,790 subjects. There was a significant discrepancy between the planned and the actual number of subjects enrolled (10,692, versus 6,790). The Applicant clarifies that the statistical power of the proposed analysis only depends on the numbers of RT-PCR confirmed influenza cases and not on the numbers of subjects enrolled.

The CHMP guideline on influenza vaccines (EMA/CHMP/VWP/457259/2014) recommends that the elderly population is stratified by age, and highlights that every effort should be made to enrol a representative sample of subjects above 75 years of age and to stratify according to age. In accordance with this requirement randomization was stratified by age (cohorts 65 to 74 years and 75 years and above).

It is considered adequate that the Primary VE analysis was based on the FAS Efficacy. Practically all subjects enrolled were exposed to the vaccine and only 2.7% of the exposed subjects did not complete the study protocol. Overall, the main reasons for exclusion of subjects from the FAS and PPS Efficacy Sets were balanced between the vaccine groups.

The overall demographic and baseline characteristics of subjects in the different sets were well balanced between the two vaccine groups with similar age, sex, ethnicity, race, and BMI. However, very few subjects (around 2%) were older than 85 years of age.

Efficacy results

Using the protocol-defined ILI, the VE against RT-PCR confirmed influenza due to any strain was 19.80% and the LL of the 97.45% CI was -5.27%. Thus, the primary objective of demonstrating the efficacy of aQIV in adults 65 years and above in protecting against any RT-PCR confirmed influenza A and/or B diseases was not met since the pre-specified statistical success criterion (the LL of the two-sided 97.45% CI of VE should exceed 40%) was not satisfied. Similarly, none of the four secondary efficacy objectives were met.

The majority of influenza cases were A/H3N2 strains and most of them (91%) were antigenically unmatched to the vaccine strain (112 out of 124 cases based on the protocol-defined ILI). Melidou et al (2017; Vaccine 35 4828–4835) analysed the influenza virus that circulated in the World Health Organization (WHO) European Region between week 40/2016 to week 5/2017. They showed that H3 virus were the predominant ones, in agreement with the cases observed from trial V118_18. However, Melidou et al found that around 66% of the H3 cases were antigenically similar to the H3 vaccine component. The Applicant hypothesized of this discrepancy by the fact that Melidou et al may have performed the antigenic typing testing against the cell-propagated A/Hong Kong/4801/2014 strain. The circulating A/H3N2 strains matched the cell-propagated reference strain but not the egg-propagated reference strain. The Applicant did not perform studies to confirm this. In addition, it is also discussed the fact that Melidou et al could not type one third of the H3 viruses from influenza cases whereas this problem was not seen by the Company. The Company considers that this different result could have been due to the fact that Meliodou et.al. used an HI analysis whereas the Company used a MN assay for antigenic classification. The Applicant did not perform studies to confirm this.

An observation made in this study was that the clinical criteria used to define influenza-like illness appears to have an impact on the estimated efficacy of aQIV. The protocol of the trial specified the primary ILI case definition, and the modified CDC ILI. A post-hoc analyses was then performed using the standard CDC ILI and WHO ILI definitions. The protocol defined ILI was the most sensitive among the different ILI definitions used but with a low specificity. As all cases were confirmed to be influenza by RT-PCR, it is likely that this ILI definition captured milder disease, associated with less fever and symptomatology. As the specificity of the ILI case definition increased to that of the WHO (the ILI definition with the highest specificity- requiring fever ≥38°C), the magnitude of benefit of the aQIV vaccine increased. Importantly, VE in all these comparisons did not meet the success criterion for the primary endpoint. It is not straightforward to get any conclusion from these analyses using different ILI definitions, but overall these results appear to show moderate efficacy against any RT-PCR confirmed influenza.

Subgroup analyses by age, comorbidity score, previous vaccination status, smoking status, sex, race and country was conducted for the primary and the secondary efficacy endpoints. There were no notable subgroup differences in the VE of aQIV observed by age, comorbidity score, previous vaccination, smoking status, sex, and race. While there may be some subgroups that tended to show higher or lower VE, the CIs were generally overlapping. Other subgroups were too small to draw any meaningful conclusions.

The subgroup analyses made by country revealed that some subgroups have different VEs. In fact, some countries the Philippines (62.45% [95% CI: 18.81%, 82.64%]), Latvia (53.44 [-86.91, 88.40]) and Estonia (50.94% [95% CI: 6.41%, 74.28%]) showed higher VE estimates than others. It could be observed that most confidence intervals were generally overlapping. The study was not designed to estimate vaccine efficacy at country level. Nevertheless, the Applicant have carried out an exploratory analysis that shows that there is a correlation between the genetic distance of the circulating strains compared to the vaccine strains, which is smaller in those countries with a higher VE. The Applicant also mention that the circulation of different influenza virus types (A/H1N1, A/H3N2 or B) in each of these countries is another possible reason for the observed inter-country differences in vaccine efficacy.

During this procedure, the US Food and Drug Administration (FDA) has approved the aQIV for use in adults 65 years of age and older, with a postmarketing requirement to conduct study V118_24, a clinical disease endpoint trial in subjects 65 years of age and older with Fluad Quadrivalent (this is the tradename of Fluad Tetra in the US). This study is planned be completed in March 31, 2024. Given that the efficacy study V118_18 has failed to meet its primary endpoint, the CHMP would benefit from reviewing the data derived from this planned study (clinical recommendation).

Immunogenicity results

It was shown that Fluad Tetra elicited a robust immune response against all four strains (in terms of GMTs and seroprotection rates) contained in the vaccine which met CBER criteria of sufficient immunogenicity for this age group.

Subgroups (age, comorbidity status, previous vaccination, gender, and race) confirmed adequate immune response of aQIV in subjects of different age groups (≥ 65-74, ≥ 75-84, ≥ 85 years), comorbidity status, previous influenza vaccination history, gender and race. When the analysis was done according to previous vaccination status it was found that subjects who were not vaccinated with an influenza vaccine in the past 5 years, had lower GMTs at Day 1 for all strains, compared to those who were vaccinated. However, at Day 22, post-vaccination GMTs were consistently higher for all strains in subjects without previous influenza vaccination in the aQIV group. The GMRs for subjects in the aQIV group were consistently higher for all strains in subjects without previous influenza vaccination. The Company considers that the higher post vaccination titres observed against B strains in subjects without previous influenza vaccination can be explained by the fact that a lower postvaccination HI titers may have been reached in subjects receiving repeated annual vaccination with unaltered B vaccine strains. This explanation is considered sensible.

Concomitant administration (aTIV)

There is currently no data on concomitant administration of Fluad Tetra with other vaccines.

Effectiveness studies

The Applicant has presented two effectiveness studies that compare the performance of aTIV versus TIV in the real-world situation.

Study C70P1 was carried out in Italy during three influenza seasons (2006/2007 through 2008/2009). The study objectives were to assess the relative risk of hospitalizations for influenza or pneumonia

during the influenza season amongst subjects ≥65 years of age who received either aTIV or non-adjuvanted TIV. One important caveat that this study presents is that there is no laboratory confirmation of influenza cases. Also, the Applicant explains that in general the health care providers administered aTIV to subjects with worse baseline health status than those subjects who received TIV. Although the confounding variables have been adjusted to try to avoid biases in the conclusions of the study, the reliability of the results from this study is not clear.

Study V70_49OBTP was carried out in Canada to assess vaccine effectiveness of aTIV versus a nonadjuvanted TIV (standard TIV predominantly Fluviral), or no vaccination. In this study there was a PCR confirmation of all ILI cases, but very few subjects participated as to have reliable results. Of all the subjects, 89% reported at least one chronic disease, but as there were different categories of chronic diseases, an adjustment for confounding variables was carried out. After the adjustment, the absolute vaccine effectiveness for aTIV was 58% (95% CI: 5%, 82%; P < 0.04) whereas non-adjuvanted TIV was ineffective compared to no vaccination. The Applicant's explanation for the non-effectiveness of the non-adjuvanted TIV is that influenza vaccine effectiveness (IVE) varies responding to complex factors and that in recent years there are multiple examples of IVE estimates showing little or no effectiveness, especially for H3N2 strains. Also, for all figures presented from this study the lower limit for the confidence intervals are very low (probably due to the low number of participants), and thus the results should be considered with caution.

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

2.5.9. Conclusions on the clinical efficacy (elderly indication)

Overall, the study design of the pivotal efficacy trial V118_20 was in agreement with the CHMP guideline on influenza vaccines (EMA/CHMP/VWP/457259/2014) and it was considered adequate.

In terms of immunogenicity, the primary endpoint was met, and showed that aQIV elicited a non-inferior immune response as compared to aTIV-1 and aTIV-2 in terms of GMT ratios and differences in SC rates. Additionally, the secondary endpoint regarding immunologic superiority of aQIV relative to aTIV for the alternate B strain was also met.

The trial V70_27 was also considered adequate. In study (V70_27), the first (lot-to-lot consistency) and third (non-inferiority according to CHMP criteria) co-primary objectives were met. Regarding the second co-primary objective, non-inferiority of aTIV relative to TIV was demonstrated against the 3 homologous influenza strains according to CBER criteria, but superiority of aTIV to TIV for at least 2 homologous strains was not demonstrated. In a posthoc analysis, it was shown that aTIV elicited significantly higher GMT levels and SCR than TIV against all 3 homologous strains, demonstrating the benefit of the MF-59 adjuvant in subjects ≥65 years of age.

The immunogenicity of Fluad (trivalent formulation) is relevant to Fluad Tetra because both vaccines are manufactured using the same process and have overlapping compositions.

Regarding absolute efficacy trial V118_18, The pre-specified success criterion to demonstrate VE of aQIV against any RT-PCR confirmed influenza cases (primary efficacy objective) was not met as the LL of the 95% CI of VE estimates did not exceed 40%. The pre-specified success criterion to demonstrate VE of aQIV against antigenically matched influenza cases (key secondary efficacy objective) was also not met given the low number of matched cases as the LL of the 95% CI of VE estimates did not exceed 40%. aQIV provided higher VE, with lower bounds above zero when the modified CDC ILI and standard CDC ILI definitions were used.

It should be noted that during this procedure, the US Food and Drug Administration (FDA) has approved the aQIV for use in adults 65 years of age and older, with a postmarketing requirement to conduct study V118_24, a clinical disease endpoint trial in subjects 65 years of age and older with Fluad Quadrivalent (this is the tradename of Fluad Tetra in the US). This study is planned to be completed in March 31, 2024. Given that the efficacy study V118_18 has failed to meet its primary endpoint, the CHMP would benefit from reviewing the data derived from this planned study. Therefore, the Clinical Study Report from study V118_24 will be added as a recommendation.

In conclusion, it is considered that an indication for elderly can be granted.

2.6. Clinical safety (paediatric indication)

Patient exposure

Assessment of the aQIV safety profile in children is primarily based on 1 pivotal study in children 6 to <72 months of age (Study V118_05) and further supported by 6 aQIV/aTIV studies and 2 aQIV revaccination studies. There are three main sets of pooled safety data on which the applicant has based its discussion of safety

- Pivotal Pooling
- Supportive Pooling
- Revaccination studies

In the pivotal aQIV study V118_05, 5,339 subjects were exposed to aQIV. Of these, the following season 317 were revaccinated with aQIV in study V118_05E1 and 403 in study V118_05E3. In addition, 402 subjects exposed to non-adjuvanted comparator in V118_05 were vaccinated with aQIV in the revaccination study V118_05E3.

In the 6 supportive studies, 3,123 subjects from study V70_29 with aTIV were included in the Pivotal Pooling, and 546 subjects from the 5 additional supportive studies with aQIV/aTIV (V70_50, V70P2, V70P6, V70_34, and V104P2) were included in the Supportive Pooling.

In the 3 aQIV clinical studies, safety and tolerability was determined by the collection of solicited local and systemic adverse events (AEs) for 7 days after each vaccine dose; and any unsolicited AE during the treatment period (Day 1 to 21). Occurrence of SAEs, AEs leading to study withdrawal, AESIs, and AEs leading to a new onset of chronic disease (NOCD) were monitored for up to 12 months after receipt of the last dose of study vaccine. All solicited and unsolicited AEs are summarized individually for Studies V118_05, V118_05E1, and V118_05E3.

Unsolicited AEs are summarized for the 3 aQIV studies individually through a general overview of these events, including severity and causality, and more detailed Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) analyses of frequent AEs (≥2% total incidence for pooled data).

Studies V118_05 and V70_29 comprise the Pivotal Pooling analysis that provides the key safety data to support the use of aQIV in paediatric subjects. The Pivotal Pooling analysis provides safety data across 15,208 subjects from 6 to <72 months of age, with 8,462 unique subjects having been exposed to aQIV or aTIV. The key pooled safety data presented include SAEs, AEs leading to withdrawal, AEs following immunization (AEFIs), AESIs, and NOCDs. Both studies had a 12-month follow-up period after vaccine administration, as well as prospective AESI collection.

The Supportive Pooling analysis includes 1,099 subjects 6 to <72 months of age of whom 546 were vaccinated with aQIV or aTIV across 5 clinical studies. The Supportive Pooling included studies in which safety evaluations were performed in a similar manner as for the pivotal studies, follow-up periods for studies in the Supportive Pooling analyses were up to 6 months.

Overall, 6,483 subjects were exposed to aQIV throughout the clinical studies; 3,647 subjects were exposed to the trivalent formulation aTIV and 7,692 to a comparator vaccine.

All unsolicited AEs that occurred, regardless of investigator causality assessment, were included in the (pooled) analyses. Pivotal Pooling and Supportive Pooling summaries are provided for AEs including deaths, AEs leading to withdrawal, SAEs, AESIs, and AEFIs; NOCDs are reported for Pivotal Pooling only.

All pooled studies applied the dosing recommendations from the WHO i.e., children less than 3 years of age received a 0.25 mL dose of aQIV or aTIV (or non-adjuvanted comparator) containing 7.5 µg of influenza virus HA for each of the 3 or 4 influenza strains. Children ≥3 years of age received a 0.5 mL dose of aQIV or aTIV (or non-adjuvanted comparator), containing 15 µg of HA per influenza strain.

Adverse events

Pivotal Study V118_05

In the overall population (subjects 6 to <72 months of age), a higher proportion of subjects in the aQIV group had at least one solicited AE compared to the non-adjuvanted vaccine group after any vaccination (72.95% vs. 64.12%, respectively). The same pattern was also observed for any solicited local AEs, systemic AEs or other indicators of reactogenicity (use of antipyretics/analgesics). The majority of subjects reported local and systemic AEs that were of mild or moderate severity and resolved within 3 to 4 days. Only a small percentage (<1% for local and <5% for systemic events) of solicited AEs persisted after 7 days and there were no differences between aQIV and the comparator.

Table 53: study V118_05 – subjects with at least one soliciated adverse event, report from 6 hours through day 7, after any vaccination in subjects 6 to <72 months of age – solicited safety set

		aQIV N=5138	Comparator N=5056
After any vaccination		n (%)	n (%)
Any	**Any**	**3748 (72.95)**	**3242 (64.12)**
	None	1390 (27.05)	1814 (35.88)
Local	**Any**	**2651 (51.60)**	**2188 (43.28)**
	None	2484 (48.35)	2866 (56.69)
Systemic	**Any**	**2714 (52.82)**	**2174 (43.00)**
	None	2424 (47.18)	2881 (56.98)
Others	**Any**	**1536 (29.89)**	**907 (17.94)**
	None	3317 (64.56)	3765 (74.47)

Source: CSR V118_05, Table 14.3.1.1.

Abbreviations: aQIV = adjuvanted quadrivalent influenza vaccine; Comparator = trivalent influenza vaccine (TIV-1) in Season 1 and quadrivalent influenza vaccine 1 (QIV-1) in Season 2; n = number of subjects with values in category; N = total number of subjects.

Others include any use of antipyretics/analgesic for prevention or treatment of pain and/or fever.

Solicited Local AEs

The most frequently reported solicited local AEs in both vaccine groups in the overall age population of tenderness and erythema. The proportion of subjects with any tenderness was higher in the aQIV group (43.19%) than in the comparator group (33.86%). The proportion of subjects with erythema was similar in each age group for both vaccine groups.

A slightly higher proportion of subjects experienced moderate or severe tenderness, erythema or induration after aQIV as compared to the comparator vaccine.

Solicited Systemic AEs

The most frequently reported solicited systemic AEs reported were irritability, sleepiness and change in eating habits in both vaccine groups. The proportion of subjects with reported irritability, sleepiness and change in eating habits was slightly higher in aQIV than comparator vaccine group (27.07% vs. 22.52% for irritability, 26.25% vs. 21.25% for sleepiness, and 22.53% vs. 17.49% for change in eating habits). The proportion of subjects reporting severe irritability (1.30% aQIV vs. 0.81% comparator), sleepiness (0.76% aQIV vs. 0.38% comparator), and change in eating habits (0.97% aQIV vs. 0.95% comparator) was low in both vaccine groups. Other solicited less frequent systemic AEs were diarrhoea, vomiting and chills, with frequencies slightly higher in aQIV than comparator vaccine group.

A greater proportion of subjects experienced fever ≥38°C from 6 hours through Day 7 after any vaccination in the aQIV group than in the comparator vaccine group (19.1% vs. 10.5%). The majority of subjects with fever in both vaccine groups had body temperature <39°C. A fever ≥39.0°C to <40°C was reported in 4.1% of subjects in the aQIV group and 2.3% of subjects in the comparator vaccine group. Overall, only a small proportion of subjects had high fever ≥40°C, which was similar for both vaccine groups (0.4% aQIV, 0.3% comparator vaccine group).

Solicited AEs after First and Second Vaccination

Within each vaccine group, the proportion of vaccine-naive subjects with any solicited AE was slightly lower after Vaccination 2 as compared to after Vaccination 1 (54.07% vs. 63.45% for aQIV and 43.45% vs. 55.14% for comparator group).

Tenderness was less frequently reported after Vaccination 2 than after Vaccination 1 in both vaccine groups: 27.76% vs. 32.20% with aQIV and 21.07% vs. 24.82% with comparator vaccine. For systemic AEs, irritability and sleepiness were less frequently reported after Vaccination 2 than after Vaccination 1 for both vaccine groups (irritability: 16.74% vs. 22.06% for aQIV and 13.04% vs. 18.71% for comparator group; sleepiness: 15.02% vs. 21.16% for aQIV and 10.49% vs. 17.98% for comparator, after Vaccination 2 and 1, respectively).

The proportion of vaccine-naive subjects with fever (defined as ≥38°C) was similar after Vaccination 2 and Vaccination 1 for both vaccine groups, and as well as after the first vaccination was higher in the aQIV group (14.4% vs. 13.1% for aQIV and 6.8% vs. 7.1% for the comparator after Vaccination 2 and Vaccination 1, respectively). The proportion of subjects with high fever ≥40°C was similar after Vaccination 2 and Vaccination 1 for both groups (0.3% vs. 0.2% for the aQIV group and 0.2% vs. 0.2% for the comparator vaccine group). The use of antipyretics/analgesics was similar after Vaccination 2 and Vaccination 1 for both vaccine groups and higher in the aQIV group.

Revaccination Study V118_05E1

Overall, a higher proportion of subjects in the aQIV group than in the QIV-1 group had at least one solicited AE between 6 hours and 7 days after vaccination (63.72% vs. 51.39%, respectively). The majority of subjects experiencing local and systemic AEs reported events that were mild to moderate in severity and resolved within 4 days.

The most frequently reported solicited local AEs in both vaccine groups after revaccination were tenderness, erythema and induration. The proportion of subjects with tenderness, erythema and induration was higher in the aQIV group than in QIV-1 group (46.69% vs. 28.15% for tenderness, 9.93% vs. 3.33% for erythema, and 7.28% vs. 2.59% for induration).

The most frequently reported solicited systemic AEs reported were irritability, sleepiness and change in eating habits in both vaccine groups. The proportion of subjects with reported irritability, sleepiness and change in eating habits was higher in aQIV than QIV-1 (26.82% vs. 16.67% for irritability, 24.50% vs. 19.63% for sleepiness, and 17. 88% vs. 10.37% for change in eating habits). The proportion of subjects reporting severe irritability, sleepiness, and change in eating habits was low in both vaccine groups (0.33% and 0% for irritability, 1.66% and 0% for sleepiness, and 0.99% and 0.37% for change in eating habits).

A greater proportion of subjects experienced fever ≥38°C from 6 hours through Day 7 after any vaccination in the aQIV group than in the QIV-1 group (9.8% vs. 4.5%). High fever ≥40°C was reported in 1 subject in the aQIV group, who experienced a febrile convulsion on Day 6.

The use of analgesic or antipyretic medication for treatment was reported by 19.39% of aQIV subjects and 7.22% of comparator subjects. These results are concordant with those of the pivotal study.

Revaccination Study V118_05E3

The incidence of solicited AEs in the revaccination study V118_05E3 was greater in subjects who received aQIV compared to QIV-1, regardless of the vaccine allocation (aQIV or non-adjuvanted comparator) in Study V118_05.

Overall, a higher proportion of subjects in the aQIV/aQIV group than in the QIV-1/QIV-1 group had at least one solicited AE between 6 hours and 7 days after vaccination (64.76% vs. 40.71%, respectively). The same pattern was observed for any solicited local AEs, systemic AEs or Others (use of antipyretics/analgesics).

The most frequently reported solicited local AE across all four groups after revaccination was tenderness. For 8 subjects, the tenderness was reported as severe (5 [1.24%] subjects in the aQIV/aQIV group, 2 [0.50%] subjects in the aQIV/QIV-1 group, and 3 [0.75%] subjects in the QIV-1/aQIV group). No subject in the QIV-1/QIV-1 group reported tenderness as severe.

Fever (body temperature ≥38°C) was the most commonly reported solicited systemic AE and occurred more frequently in subjects who received aQIV (aQIV/aQIV: 21.59%; QIV-1/aQIV: 11.69%) than in subjects who received QIV-1 (aQIV/QIV-1: 7.44%; QIV-1/QIV-1: 7.38%). High fever ≥40.0°C was rare and experienced by 1 subject each group except for the aQIV/QIV-1 group (no subjects).

Sleepiness was the solicited systemic AE experienced with the next highest frequency in any treatment group after fever (aQIV/aQIV: 19.35%; aQIV/QIV-1: 11.17%; QIV-1/aQIV: 13.68%, QIV-1/QIV-1: 6.11%). Irritability and change in eating habits followed a similar pattern to that seen for sleepiness, in that the subjects in the aQIV treated groups experienced these events more frequently than those in the QIV-1 treated groups. The proportion of subjects reporting severe sleepiness, irritability, and change in eating habits was low and occurred only in treatment groups that included aQIV (sleepiness: aQIV/aQIV: 0.50%; irritability: aQIV/aQIV: 0.50%; change in eating habits: aQIV/aQIV: 0.99%, aQIV/QIV-1: 0.25%). No subjects in the QIV-1/QIV-1 group experienced severe sleepiness, irritability or change in eating habits.

In the overall study population, use of analgesic or antipyretic medication for prevention from 6 hours through Day 7 was reported by 9.23% of aQIV/aQIV subjects, 4.14% of aQIV/QIV-1 subjects, 6.35% of QIV-1/aQIV subjects, and 4.80% of QIV-1/QIV-1 subjects. The use of analgesic or antipyretic medication

for treatment in this time frame was reported by 22.69% of aQIV/aQIV subjects, 8.56% of aQIV/QIV-1 subjects, 13.81% of QIV-1/aQIV subjects, and 7.91% of QIV-1/QIV-1 subjects.

In the CSR of study V118_05E3 the AEs for the pooled vaccine groups, i.e. according to the treatment allocation in this study irrespective of that in the parent study, are presented.

	Pooled aQIV/aQIV & QIV/aQIV N=805	Pooled aQIV/QIV & QIV/QIV N=796
	n (%)	n (%)
Any	476 (59.13)	362 (45.48)
Local	328 (40.75)	269 (33.79)
Systemic	282 (35.03)	174 (21.86)
Other*	179 (22.24)	82 (10.30)

Source: Table 14.3.1.4.9
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; N=total number of subjects; n=number of subjects with values in category; QIV=quadrivalent influenza vaccine
*Other refers to the answer to the question: "Did the subject use any Analgesic/Antipyretic medication for prevention or treatment of pain and/or fever?" and is referred to as 'General' in the source tables.
Treatments: aQIV/aQIV=Arm A, aQIV/QIV=Arm B, QIV/aQIV=Arm C, QIV/QIV=Arm D.

shows the proportion of subject with at least one solicited adverse event pooled data, where it can be seen that a proportion of any solicited local, or systemic events as well as fever an antipyretics use is higher in the pooled aQIV group then the QIV groups.

Table 54: number and proportion of subjects with at least one solicited adverse event, reported between 6 hours and day 7 after vaccination by pooled treatment group – solicited safety set

	Pooled aQIV/aQIV & QIV/aQIV N=805	Pooled aQIV/QIV & QIV/QIV N=796
	n (%)	n (%)
Any	476 (59.13)	362 (45.48)
Local	328 (40.75)	269 (33.79)
Systemic	282 (35.03)	174 (21.86)
Other*	179 (22.24)	82 (10.30)

Source: Table 14.3.1.4.9
Abbreviations: aQIV=adjuvanted quadrivalent subunit influenza virus vaccine; N=total number of subjects; n=number of subjects with values in category; QIV=quadrivalent influenza vaccine
*Other refers to the answer to the question: "Did the subject use any Analgesic/Antipyretic medication for prevention or treatment of pain and/or fever?" and is referred to as 'General' in the source tables.
Treatments: aQIV/aQIV=Arm A, aQIV/QIV=Arm B, QIV/aQIV=Arm C, QIV/QIV=Arm D.

Unsolicited Adverse Events

Pivotal Study V118_05

In the overall age group (6 months to <72 months), the proportion of subjects with any unsolicited AEs was similar for the aQIV and comparator groups (68.21% vs. 68.65%).

The most commonly reported AEs and related AEs according to SOC were 'general disorders and administration side conditions', and 'infections and infestations' during the overall and treatment period. The proportion of subjects reporting unsolicited AEs was similar for the vaccine groups (68.21% vs. 68.65% during overall period, and 49.91% vs. 50.05% during treatment period, for the aQIV and comparator groups, respectively).

The most frequently reported unsolicited AEs in either vaccine group during the overall period and treatment period were influenza-like illness (ILI) (51.34% in aQIV group and 51.66% in comparator vaccine group during overall period; 19.57% vs. 18.47% during treatment period) and upper respiratory tract infection (9.78% vs. 10.54% during overall period; 9.77% vs. 10.46% during treatment period). The majority of unsolicited AEs in either group were mild in severity.

The proportion of possibly related unsolicited AEs was 13.08% for the aQIV group and 10.33% for the comparator in the overall period and 12.76% for the aQIV group vs. 10.08% for the comparator during the treatment period.

The most frequently reported related unsolicited AE was ILI in both vaccine groups (5.95% and 4.20% during overall period, 5.59% and 3.93% during treatment period. The majority of unsolicited AEs considered related to the study vaccine during both the overall and treatment periods were mild in severity.

Table 55: **Study V118_05 – Overview of Unsolicited Adverse Events Reported After Any Vaccination – overall Period – Unsolicited Safety Set**

	aQIV N=5243 n (%)	Comparator N=5161 n (%)
Any unsolicited AEs	**3576 (68.21)**	**3543 (68.65)**
Possibly or probably related AEs	686 (13.08)	533 (10.33)
Any SAEs	234 (4.46)	230 (4.46)
Possibly or probably related SAEs[a]	6 (0.11)	1 (0.02)
Any AEs with an outcome of death	1 (0.02)	3 (0.06)
Any AEs leading to premature study withdrawal	10 (0.19)	9 (0.17)
Any AEs leading to NOCD	87 (1.66)	96 (1.86)
Any AESI	5 (0.10)	4 (0.08)

Source: CSR V118_05, Table 14.3.1.13, Table 14.3.1.16, Table 14.3.2.1, Table 14.3.2.2, Table 14.3.2.3, Table 14.3.2.4, Table 14.3.2.6, Table 14.3.2.8.

Abbreviations: AE = adverse event; AESI = adverse events of special interest; aQIV = adjuvanted quadrivalent influenza virus vaccine; Comparator = trivalent influenza vaccine 1 (TIV-1) in Season 1 and quadrivalent influenza vaccine 1 (QIV-1) in Season 2; n = number of subjects with values in category; N = total number of subjects; NOCD = new onset of chronic disease; SAE = serious adverse event.

[a] According to the investigator.

Revaccination Study V118_05E1

Unsolicited AEs were reported in a comparable proportion of subjects in the aQIV group (56.47%) and the QIV-1 group (52.08%) during the total study period. The proportion of subjects reporting AEs was generally comparable between vaccine groups on a SOC and PT level.

In the treatment period, unsolicited AEs were reported in a slightly higher proportion of subjects in the aQIV group than in the QIV-1 group (26.81% vs. 20.83%), but the proportion of subjects reporting related AEs was similar between vaccine groups (15 [4.73%] for aQIV and 15 [5.21%] for QIV-1). The most frequently reported AEs in treatment period in either vaccine group were upper respiratory tract infection (15 [4.73%] vs. 9 [3.13%]) and ILI (13 [4.10%] vs. 16 [5.56%]).

Revaccination Study V118_05E3

In revaccination Study V118_05E3, during the total study period, unsolicited AEs were reported in a comparable proportion of subjects in all treatment groups (reported for 52.16% to 55.97% of subjects). The proportion of subjects reporting AEs was generally comparable between treatment groups on a SOC and PT level.

A small proportion of subjects across all groups experienced unsolicited AEs, which were considered by the investigator to be at least possibly related to the vaccination: from 3.82% (QIV-1/QIV-1) to 6.20% (aQIV-1/aQIV-1) of subjects.

Table 56: Study V118_05E3 – Overview of Unsolicited Adverse Events Reported After Any Vaccination in All Subjects, Overall Period – Unsolicited Safety Set

Category	aQIV/aQIV	aQIV/QIV-1	QIV-1/aQIV	QIV-1/QIV-1
	N=403	N=403	N=402	N=393
	n (%)	n (%)	n (%)	n (%)
At least one unsolicited AE	**218 (54.09)**	**223 (55.33)**	**225 (55.97)**	**205 (52.16)**
At least one possibly or probably related unsolicited AE	25 (6.20)	16 (3.97)	23 (5.72)	15 (3.82)
At least one unsolicited severe AE	4 (0.99)	5 (1.24)	5 (1.24)	4 (1.02)
At least one unsolicited AE leading to study withdrawal and early termination	0	0	0	0
At least one SAE	10 (2.48)	11 (2.73)	7 (1.74)	8 (2.04)
At least one possibly or probably related SAE	0	0	0	0
Medically attended unsolicited AE[a]	208 (51.61)	219 (54.34)	217 (53.98)	191 (48.60)
At least one unsolicited AE leading to NOCD after vaccination	2 (0.50)	0	0	0
At least one AESI	0	0	0	1 (0.25)
AEs leading to death	0	0	0	0

Source: CSR V118_05E3, Table 14.3.1.11, Table 14.3.1.11.3, Table 14.3.1.11.4, Table 14.3.2.1, Table 14.3.2.2, Table 14.3.2.3, Table 14.3.2.5, Table 14.3.2.6, Table 14.3.2.7 and Table 14.3.2.8.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CRF = case report form; aQIV = adjuvanted quadrivalent influenza vaccine; n = number of subjects with values in category; N = total number of subjects; NOCD = new onset chronic disease; SAE = serious adverse event; QIV-1 = quadrivalent influenza vaccine 1.

[a] AEs leading to an unscheduled visit to a healthcare practitioner and/or an emergency room visit were to be reported as 'Medically Attended AE' on a separate CRF entry.

The most frequently reported AEs in this period in either treatment group were upper respiratory tract infection (4.33% to 4.73%) and ILI (5.34% to 6.72%).

In the treatment period, severe events were reported in 2 subjects: 1 subject with injection site erythema and injection site pain in the aQIV/QIV-1 group and 1 subject with gastroenteritis in the QIV-1/aQIV group. The injection site erythema and injection site pain were considered probably related and the gastroenteritis was unrelated to the study vaccine.

Serious adverse event/deaths/other significant events

A total of 13 SAEs with the outcome of death in paediatric subjects 6 to <72 months of age were reported in 3 of the 9 clinical studies included in this safety summary (4 in V118_05, 8 in V70_29, and 1 in V70P6). Only 2 deaths occurred from subjects in an adjuvanted vaccine group. None of the deaths were considered to be vaccine-related. Additional details about individual cases are located in the subject narratives from the respective CSRs.

Other Serious Adverse Events

Study V118_05

The majority of SAEs in Study V118_05 were reported in the SOC Infections and infestations (Table 2-22). Overall, the proportion of subjects with SAEs was similar for the aQIV and comparator vaccine groups (234 [4.46%] subjects vs. 230 [4.46%] subjects) during the overall period. The most frequently reported SAEs were pneumonia (38 [0.72%] and 28 [0.54%]), gastroenteritis (23 [0.44%], 23 [0.45%]) and animal bite (24 [0.46%], 19 [0.37%]). During the treatment period, the proportion of subjects with SAEs was similar for the aQIV and comparator vaccine groups (41 [0.78%] subjects vs. 44 [0.85%], respectively).

Related SAEs

Related SAEs were reported in 6 subjects in aQIV group and in 1 subject in comparator vaccine group.

The 6 SAEs in the aQIV group included Type I hypersensitivity, febrile convulsion, allergy to arthropod bite, anaphylactic reaction, hypersensitivity, and papule. The possibly related SAE in the QIV-1 group included diarrhoea and vomiting.

Pivotal Pooling

An overview of unsolicited AEs leading to withdrawal, AEs with outcome of death, SAEs, AESIs, NOCDs, and AEFIs reported by subjects included in the Pivotal Pooling is provided in Table 58 below for subjects from 6 to <72 months of age.

Table 57 Pivotal pooling – Overview of AE and SAE, including Risk Ratios, in All Subjects-Safety Set

Variable	aQIV/aTIV Pool N=8462 n (%)	QIV-1/TIV-1 Pool N=6746 n (%)	Risk Ratio (95% CI)	p-value
Any SAE - overall period	349 (4.1)	294 (4.4)	0.92 (0.79-1.08)	*0.3244*
Any SAE - treatment period	67 (0.8)	55 (0.8)	0.95 (0.66-1.35)	*0.7616*
Any related SAE - overall period	7 (0.1)	1 (0.0)	5.94 (0.73-48.56)	*0.0968*
Any AE leading to WD	11 (0.1)	14 (0.2)	0.71 (0.32-1.56)	*0.3922*
Any related AE leading to WD	7 (0.1)	3 (0.0)	2.31 (0.60-8.93)	*0.2257*
Any AE with outcome death	2 (0.0)	6 (0.1)	0.27 (0.05-1.34)	*0.1095*
Any related AE with outcome death	0	0	-	-
Any AESI	7 (0.1)	5 (0.1)	1.15 (0.36-3.62)	*0.8176*
Any NOCD	135 (1.6)	128 (1.9)	0.84 (0.66-1.07)	*0.1502*
Any AEFI	20 (0.2)	12 (0.2)	1.35 (0.66-2.77)	*0.4113*
Hypersensitivity	16 (0.2)	11 (0.2)	1.20 (0.56-2.59)	*0.6436*
Febrile convulsion[a]	4 (0.0)	1 (0.0)	2.94 (0.33-26.33)	*0.3352*

Source: Appendix 1, Table T11P.13.0.0.

Abbreviations: AE = adverse event; AEFI = adverse event following immunization; AESI = adverse event of special interest; aQIV = adjuvanted quadrivalent influenza vaccine; aTIV = adjuvanted trivalent influenza vaccine; CI = confidence interval;MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects with values in category; NOCD = new onset of chronic disease; PT = preferred term; QIV-1 = quadrivalent influenza vaccine 1; SAE = serious adverse event; SMQ = standardized MedDRA query; TIV-1 = trivalent influenza vaccine 1; WD = withdrawal.

The category of related AEs is formed by both possibly and probably related AEs.

Risk ratios are presented as aQIV/aTIV group divided by QIV-1/TIV-1 group for AEs with total incidence ≥5 and were calculated using a Poisson regression model with logarithmic link function, adjusted for the number of days in study and the number of vaccines given.

[a] Database was searched using pre-identified PTs from the narrow SMQ "Generalized convulsive seizure following immunization" but identified AEFI cases were all PT Febrile convulsion.

Note: percentages of <0.1% are displayed as 0.0%.

In total, 643 out of 15,208 subjects in the Pivotal Pooling experienced at least one SAE (4.1% aQIV/aTIV group and 4.4% QIV-1/TIV-1 group).

From 643 SAES 8 were assessed by the investigator as related to the vaccine and the vast majority, 7, were in the aQIV/aTIV group and only 1 the pooled QIV-1/TIV-1 group. However, risk ratios did not indicate a statistically significant difference between aQIV/aTIV and QIV 1/TIV 1 regarding frequency of overall SAEs in all subjects. All individual SAEs (by PT) occurred in less than 1% of the subjects in either vaccine group.

The most frequently reported SAEs were pneumonia (68 [0.8%] and 47 [0.7%]), animal bite (46 [0.5%], 33 [0.5%]), and gastroenteritis (41 [0.5%], 35 [0.5%]). All other SAEs occurred in less than 0.5% in either vaccine group.

In the pivotal pooling the risk ratios of SAEs by PT did not show an increased risk for the individual SAEs after vaccination with aQIV/aTIV as compared with QIV 1/TIV 1 except for Febrile convulsion (Nervous System Disorders) that showed a risk ratio of 1.85, and 95% CI 0.89-3.85 (*p* value 0.0981).

Of the febrile convulsions that were reported as an SAE, 4 of the cases (<0.1%) occurred in the treatment period (3 aQIV/aTIV and 1 QIV 1/TIV 1).

Related SAEs

In the overall population of subjects from 6 to <72 months of age, 8 subjects (at most 0.1% per vaccine group and overall) reported SAEs during the overall period that were considered by the study investigator to be at least possibly related to the study. Although there were no statistically significant differences in relative risk between aQIV/aTIV and QIV-1/TIV-1 for subjects with related SAEs, 7 subjects were in the aQIV/aTIV group (allergy to arthropod bite, anaphylactic reaction, hypersensitivity, Type I hypersensitivity, Type III immune complex mediated reaction, febrile convulsion, and papule) and 1 subject in the QIV-1/TIV-1 group (diarrhoea and vomiting [both events in the same subject]).

Revaccination Study V118_05E1

Eleven subjects experienced SAEs in the revaccination study V118_05E1; 7 (2.21%) subjects in the aQIV group, and 4 (1.39%) subjects in the QIV-1 group. None of the SAEs were reported in the treatment period and none of the SAEs were considered to be related to the study vaccine.

Revaccination Study V118_05E3

There were 36 subjects who experienced SAEs in revaccination study V118_05E3. For those who received aQIV in the revaccination study, 10 subjects (2.48%) in the aQIV/aQIV group and 7 subjects (1.74%) in the QIV-1/aQIV group, experienced SAEs.

For those who received QIV-1 in the revaccination study, 11 subjects (2.73%) in the aQIV/QIV-1 group and 8 subjects (2.04%) and QIV-1/QIV-1 group, experienced SAEs. None of the SAEs were considered to be related to the study vaccine.

Laboratory findings

Clinical laboratory data were collected in Study V70_29. A total of 200 subjects (99 in the aTIV group, 49 in the TIV-1 group, and 52 in the TIV-2 group) were evaluated by clinical laboratory analyses of blood samples taken at Day 1 and Day 8. Clinical chemistry and haematology laboratory toxicity assessments indicated that nearly all the subjects were at Grade 0 (none) or Grade 1 (mild) levels of toxicity for all the measures tested (91% – 100% of subjects for each measure). None of the subjects had a grade of 3 (severe) or 4 (potentially life-threatening) for any of the measures tested.

Safety in special populations

Safety from subgroup analyses includes data from Study V118_05, as this was the largest pivotal aQIV study comprising the majority of paediatric subjects.

Analyses by Age

In Study V118_05 the demographic and baseline characteristics observed in the overall population of subjects from 6 to <72 months of age were similar to that of the 2 age subgroups including subjects from 6 to <24 months of age and from 24 to <72 months of age. The younger and the older age subgroups appeared generally well balanced on demographics and baseline characteristics, with a slightly higher number of naive subjects in the 6 to <24 months of age group when compared to the older subjects (24 to <72 months). The reporting period for AEs was approximately 4 weeks longer for naive subjects (receiving 2 vaccinations 4 weeks apart) than for non-naive subjects (receiving single vaccination).

Solicited Adverse Events

For both age subgroups, 6 to <24 months and 24 to <72 months, the proportion of subjects with any solicited AEs after any vaccination was higher in the aQIV group than in the comparator group (Table 59). The vaccine group difference (aQIV vs. comparator vaccine group) was larger in the older age group.

Table 58: Study V118_05 – Subjects with at Least one Solicited Adverse Event, Report from 6 Hours through Day 7, by Vaccination in subjects 6 to <24 months and 24 to <72 months of age – Solicited Safety Set

		≥6 to <24 Months		≥24 to <72 Months	
		aQIV	Comparator	aQIV	Comparator
		n (%)	n (%)	n (%)	n (%)
After any vaccination		**N=1269**	**N=1308**	**N=3869**	**N=3748**
Any	Any	917 (72.26)	873 (66.74)	2831 (73.17)	2369 (63.21)
	None	352 (27.74)	435 (33.26)	1038 (26.83)	1379 (36.79)
Local	Any	491 (38.69)	443 (33.87)	2160 (55.83)	1745 (46.56)
	None	777 (61.23)	864 (66.06)	1707 (44.12)	2002 (53.42)
Systemic	Any	776 (61.15)	734 (56.12)	1938 (50.09)	1440 (38.42)
	None	493 (38.85)	573 (43.81)	1931 (49.91)	2308 (61.58)
Others	Any	403 (31.76)	286 (21.87)	1133 (29.28)	621 (16.57)
	None	797 (62.81)	911 (69.65)	2520 (65.13)	2854 (76.15)

Source: CSR V118_05, Table 14.3.1.1.1 and Table 14.8.1.1.

Abbreviations: aQIV = adjuvanted quadrivalent influenza vaccine; Comparator = trivalent influenza vaccine 1 (TIV-1) in Season 1 and quadrivalent influenza vaccine 1 (QIV-1) in Season 2; n = number of subjects with values in category; N = total number of subjects.

Note: 'Others' includes any use of antipyretics/analgesic for prevention or treatment of pain and/or fever.

The proportion of subjects with solicited local AEs was lower in younger subjects (6 to <24 months) than in older subjects in both vaccine groups. In both age groups, the most frequently reported solicited local AEs were tenderness and erythema.

Solicited Systemic AEs

For solicited systemic AEs, the proportion of subjects reporting events after any vaccination in the 6 to <24 months group was 61.15% in the aQIV and 56.12% in the comparator vaccine. In the 24 to <72 months age group the vaccine group difference was higher, 50.09% in the aQIV group vs. 38.42% in the comparator group.

In both age groups, the most frequently reported solicited systemic AEs after any vaccination were irritability, sleepiness and change in eating habits in both vaccine groups. For systemic events, the proportion of subjects with irritability was higher in the younger than the older subjects in both vaccine groups. The proportion of subjects with sleepiness and change in eating habits was higher in younger subjects in both vaccine groups.

Fever

For both age subgroups, a greater proportion of subjects experiencing fever ≥38°C from 6 hours through Day 7 after any vaccination in the aQIV group than in the comparator vaccine group.

In the aQIV group, the proportion of subjects with fever was 20.0% in the 6 to <24 months age group and 18.8% in post hoc 24 to <72 months age group. In the comparator vaccine group, the proportion of subjects with fever was lower in the post hoc 24 to <72 months age group older age group (9.4%) than in the 6 to <24 months group (13.6%).

The proportion of subjects with fever ≥40ºC was low for both vaccine groups in both age groups. In the 6 to <24 months of age group, 7 cases (0.6%) of fever ≥40ºC were reported in aQIV group and 4 cases (0.3%) in comparator vaccine group.

Antipyretics/analgesics

The use of antipyretics/analgesics was similar in the aQIV group for both age groups (31.76% in the 6 to <24 months age group; 29.28% in the post hoc 24 to <72 months group). In the comparator group slightly higher use was reported in the 6 to <24 months subjects, 21.87%, compared to 16.57% in the older subjects.

Unsolicited Adverse Events

During the overall period in Study V118_05, the proportion of subjects with any unsolicited AEs was higher in younger than older subjects in both vaccine groups. No notable difference was observed between aQIV and comparator vaccine in any of the age groups (Table 5-2). The same pattern, i.e., a higher proportion of related unsolicited AEs and unsolicited SAEs was observed in younger subjects. In the aQIV group the proportion of subjects with related AEs was 16.87% and 11.84% for the 6 to <24 months and 24 to <72 months age group respectively. In the comparator group the proportions were slightly lower 13.78% and 9.13%, for the same age groups respectively.

During the treatment period after any vaccination the pattern was similar and the proportion of subjects reporting unsolicited AEs was higher in the younger subjects (6 to <24 months) than in the older subjects (24 to <72 months) for both vaccine groups. There were no notable vaccine group differences for most frequently reported AEs (i.e., ILI and upper respiratory tract infection).

Analyses by Dose

For Study V118_05, subjects received a 0.25 mL vaccine dose from 6 to <36 months of age, and a 0.5 mL vaccine dose from 36 to <72 months of age.

Solicited Adverse Events

The proportion of subjects who reported at least one solicited AE was comparable in all dose groups. A greater percentage of subjects reported solicited AEs in the aQIV vs. comparator vaccine groups. The difference between vaccine groups tended to be smaller in the 0.25 mL dose group.

Unsolicited Adverse Events

The proportion of subjects with any unsolicited AEs was higher in the 0.25 mL dose group (subjects 6 to <36 months old) than the 0.5 mL dose group (subjects 36 to <72 months old) for both adjuvanted and non-adjuvanted vaccine groups. There were no notable differences between vaccine groups (aQIV vs. comparator) for any of the dose groups. The same pattern was observed for unsolicited SAEs and any unsolicited AEs leading to hospitalization.

Analyses by Sex

For any solicited AEs in study V118_05, the proportion of subjects with events was similar in males and females for both vaccine groups: 72.63% vs. 73.27% in aQIV group and 63.35% vs. 64.93% in comparator vaccine group. The same pattern i.e., no difference between male and female subjects was also observed for any solicited local AEs, systemic AEs and Others after any vaccination.

The proportion of male and female subjects with any unsolicited AE was similar in both vaccine groups (68.57% vs. 67.84% for aQIV group and 68.66% vs. 68.64% for comparator vaccine group). In line with overall results, no vaccine group differences were noted within the sex subgroups.

Analyses by Race

Solicited Adverse Events

In Study V118_05, the Overall Safety Set population comprised of predominately Asian (44.3%) and white (39.8%) subjects. For any solicited AEs, the proportion of subjects with events was higher in white subjects than Asian subjects for both vaccine groups: 77.89% vs. 72.94% in aQIV group and 71.65% vs. 61.30% in comparator vaccine group. Overall, the lowest incidence of solicited AEs reported from 6 hours through Day 7 after any vaccination was found in black or African American subjects (aQIV: 55.59%; comparator vaccine group: 48.65%). A similar pattern, i.e., higher percentages in white subjects, was observed for solicited local AEs and systemic AEs.

In both vaccine groups, a greater proportion of Asian subjects experienced fever ≥38°C from 6 hours through Day 7 after any vaccination than white subjects (aQIV: 26.37% vs. 13.53%; comparator vaccine group: 13.12% vs. 8.61%). In Asian subjects, also the use of antipyretics/analgesics was higher (Asian: 39.22% and 22.30%; white: 22.11% and 14.10% in the aQIV and comparator vaccine groups, respectively).

Unsolicited Adverse Events

The proportion of subjects with unsolicited AEs was higher in Asian subjects than white subjects for both vaccine groups: 77.91% vs. 66.44% in the aQIV group, respectively, and 74.98% vs. 69.74% in comparator vaccine group. Overall, the lowest incidence of unsolicited AEs after any vaccination during the overall period was in black or African American subjects (aQIV: 40.03%; comparator vaccine group: 42.09%). The proportion of subjects with possibly or probably related AEs was comparable for Asian and white subjects, but lower in black or African American subjects.

A similar pattern was observed for SAEs, i.e., higher percentages of reports in Asian subjects, (Asian: 7.23% and 6.56%; white: 2.34% and 2.86%; black or African American: 1.62% and 2.15% in the aQIV and comparator vaccine groups, respectively. SAEs which were considered related to study vaccine by the investigator only occurred in Asian subjects.

NOCDs occurred more frequently in white subjects (2.86% and 3.01% in the aQIV and comparator vaccine groups) than in Asian (0.60% in both vaccine groups) and black or African American subjects (1.33% and 2.30%).

Analyses by Risk of Influenza Complications

In Study V118_05, the majority of subjects were healthy (aQIV: 91.2%, comparator vaccine: 91.4%) and 8.7% of the subjects were considered to be at high risk of influenza complications (aQIV: 8.8%, comparator vaccine group: 8.6%).

For any solicited AEs, the proportion of subjects with at least one event was similar in healthy subjects and subjects at high risk of influenza complications for both vaccine groups: 73.06% vs. 71.78% in aQIV group and 63.88% vs. 66.75% in comparator vaccine group. No relevant difference between healthy and at high risk subjects, was also observed for any solicited local and systemic AEs.

The proportion of subjects with any unsolicited AEs was similar for healthy subjects and subjects at high risk of influenza complications in both vaccine groups (68.56% vs. 64.50% for aQIV group and 68.72% vs. 67.88% for comparator vaccine group). The most frequently reported unsolicited AEs in healthy subjects and subjects at high risk were ILI and upper respiratory tract infection for both vaccine groups.

Extrinsic Factors: Vaccine Naivety Status

For Study V118_05, analyses of solicited and unsolicited AE data are also provided by vaccine naivety status (i.e., whether or not a subject was reported to having had been previously vaccinated with an influenza vaccine).

Solicited Adverse Events

Overall in both vaccine groups, the most frequently reported solicited local AEs were tenderness and erythema and most frequently reported solicited systemic AEs were irritability, sleepiness and change in eating habits. Non-naive subjects tended to have somewhat more solicited local reactions, mainly tenderness (48.12% aQIV and 36.91% comparator in vaccine non-naive subjects vs. 32.20% aQIV and 24.82% comparator in vaccine naive subjects). This is in agreement with the age subgroup data and the fact that non-naive subjects tend to be older.

Similar trends in solicited systemic AEs and fever were seen as in the age subgroups, with 13.1% aQIV and 7.1% comparator for vaccine-naive subjects vs. 10.3% aQIV and 5.7% comparator for vaccine non-naive subjects reporting fever ≥38°C after first vaccination.

Unsolicited Adverse Events

The proportion of subjects with any unsolicited AEs was higher in the vaccine naive than in the vaccine non-naive subjects for both vaccine groups (overall period: 71.72% vs. 60.96% for aQIV group and 71.94% vs. 61.71% for comparator vaccine group; treatment period: 57.36% vs. 34.54% for aQIV group and 57.29% vs. 34.80% for comparator vaccine group). The reporting period for AEs was longer for naive subjects, who received 2 vaccinations, than for vaccine non-naive subjects, who only received a single vaccination.

Immunological events

Adverse Events of Special Interest (AESIs)

In the aQIV clinical studies (V118_05, V118_05E1, and V118_05E3), subjects were assessed for any new medical events or signs or symptoms that could possibly indicate a potential immune-mediated disease (AESIs). These events were prospectively defined and reported during the clinical study according to a list of medical terms as specified in the protocols, which was the same for all 3 aQIV studies.

Prospectively assessed AESIs are presented for all 3 individual aQIV studies. For the pooled data and for the revaccination studies (V118_05E1 and V118_05E3), the evaluation of AESIs was additionally conducted as a retrospective analysis using the list of MedDRA PTs (provided).

Study V118_05

In Study V118_05, 5 AESIs were reported after vaccination with aQIV (Henoch-Schönlein purpura, Crohn's disease, Type I diabetes mellitus, Kawasaki's disease and Encephalitis autoimmune) and 4 AESIs were reported after vaccination with the comparator vaccine (Type I diabetes mellitus, Henoch-Schönlein purpura, Immune thrombocytopenia and Coeliac Disease). None of the AESIs were considered related to study vaccine.

Pivotal Pooling

In the overall Pivotal Pooling population, 12 AESI cases were identified: 7 in the aQIV/aTIV group and 5 in the QIV-1/TIV-1 group. There were no statistically significant differences in relative risk between aQIV/aTIV and QIV-1/TIV-1 for subjects reporting any AESIs during the overall study period. All retrospectively determined AESIs occurred in 1 subject in each vaccine group and were considered unrelated to study vaccine.

During the retrospective assessment, 2 additional AESI cases were identified in Study V118_05 as compared to the prospective assessment. Based on the clinical context, these 2 cases were not prospectively defined by the study investigator as AESI with the following reasons. In the first instance, the retrospectively assessed AESI of Kawasaki's disease occurred in a subject who already had a history of Kawasaki's disease (reported term: 'Kawasaki's disease [sequelae from pre-existing condition]'). In the second instance, the retrospectively assessed AESI of 6th Nerve paralysis was a side effect of surgery (reported term: '6th nerve palsy right eye [side effect of surgery to remove ependymoma]').

Revaccination Studies V118_05E1 and V118_05E3

Unsolicited AESIs were prospectively reported for 2 subjects in V118_05E1 revaccination study. Immune thrombocytopenic purpura was reported for 1 subject in the aQIV group and Type I diabetes mellitus was reported for 1 subject in the QIV-1 group. Both events were not assessed by the investigator as related to study vaccine.

An unsolicited AESI, Kawasaki's disease, was prospectively reported for 1 subject (0.25%) in revaccination study V118_05E3 from the QIV-1/QIV-1 group.

Adverse Events Following Immunization (AEFIs)

The safety analyses were supplemented by a second retrospective analysis that included 2 categories of clinically important AEFIs: hypersensitivity-type events (including PTs from the SMQ Anaphylactic Reaction and Angioedema), indicated as AEFIs of 'Hypersensitivity' and Generalized Convulsive Seizures Following Immunization, indicated as AEFIs of 'Febrile Convulsion'. The identification of AEFI was restricted to the first 7 days after each vaccination for PTs from the Angioedema SMQ and from the Generalised Convulsive Seizures Following Immunization SMQ and restricted to the first 2 days after each vaccination for events from the Anaphylactic Reactions SMQ.

Pivotal Pooling

In the Pivotal Pooling, AEFIs were identified in 32 (0.2%) subjects (20 [0.2%] aQIV/aTIV and 12 [0.2%] QIV-1/TIV-1 group). In the 'Hypersensitivity' category, AEFIs were identified in 27 subjects (16 [0.2%] aQIV/aTIV and 11 [0.2%] QIV-1/TIV-1). In the 'Febrile Convulsion' category 5 subjects were identified (4 [<0.1%] in aQIV/aTIV and 1 [<0.1%] in QIV-1/TIV-1).

Hypersensitivity

The retrospective analysis of AEFI hypersensitivity largely identified non-serious events of mild to moderate urticaria (overall 22 out of 27, with 12 in the aQIV/aTIV group and 10 in the QIV-1/TIV-1 group). In addition, the following events were identified in the aQIV/aTIV group: 1 serious event of moderate urticaria; 2 related SAEs of Type I hypersensitivity and anaphylaxis; and 1 AE of angioedema. In the QIV-1/TIV-1 group, 1 event of mild pharyngeal oedema was reported.

There were only 2 events with immediate onset, both in the aQIV group. These were a Type I hypersensitivity which consisted primarily of cutaneous symptoms and without respiratory, gastrointestinal or cardiovascular symptoms and an event of anaphylaxis (both events were reported as SAEs and are detailed in the SAEs Section). The occurrence of these AEFI reactions was rare overall (<0.1%). Given the nature of these events, hypersensitivity AEFIs were not identified as a risk associated with aQIV/aTIV.

Febrile Convulsions

In the Pivotal Pooling study population, AEFIs of Febrile convulsion were identified in 5 subjects overall (4 subjects [<0.1%] in the aQIV/aTIV group and 1 [<0.1%] subject in the QIV-1/TIV-1 group).

The retrospective analysis of AEFI Febrile convulsions using the search criteria identified 3 non-serious, mild events and 2 serious, moderate events that were resolved. All subjects received 2 doses of the vaccine, with the incidence of the febrile convulsion only noted after either the first or the second dose, but not after both. Although the reported febrile convulsions were temporally associated with the vaccination, additional comorbidities were reported for 4 of the 5 cases (A/H1N1 influenza infection, herpangina, pneumonia, and otitis media) which cannot be excluded as potentially contributory to the incidence of febrile convulsion.

Supportive Pooling

In the overall Supportive Pooling study population, 5 AEFIs were identified: 3 [0.5%] in the aQIV/aTIV group and 2 [0.4%] in the TIV group. All 5 cases were reported in the 'Hypersensitivity' category as urticaria in the Skin and subcutaneous tissue disorders SOC.

None of the AEFI cases in the Supportive Pooling population occurred in the 'Febrile Convulsion' category.

Revaccination Study V118_05E1

After revaccination, 2 (0.4%) of the 543 subjects included in the safety set experienced an AEFI. One 23-month-old subject in the aQIV group experienced a febrile convulsion that started on Day 6, and one 46-month-old subject in the QIV-1 group experienced a mild urticaria that started on Day 5. Both events were considered unrelated to the study vaccine.

Revaccination Study V118_05E3

In the revaccination study V118_05E3, after revaccination, 2 (0.5%) of the 1601 subjects included in the safety set experienced an AEFI. Both cases were urticarias and 'Hypersensitivity' AEFIs. One 77-month-old Asian female subject in the aQIV/aQIV group experienced a mild urticaria that started on Day 4 that was considered related to the study vaccine. One 24-month-old Asian male subject in the aQIV/QIV-1 group also experienced a mild urticaria that started on *Day 6* that was considered unrelated to the study vaccine.

Safety related to drug-drug interactions and other interactions

The studies included in this Marketing Authorisation Application were not designed to prospectively assess interactions with concomitant vaccinations or drugs.

Discontinuation due to adverse events

Study V118_05

There were 19 subjects (10 [0.19 %] in the aQIV group and 9 [0.17%] in the comparator vaccine group) who reported AEs leading to premature withdrawal. Of these 19 subjects, 11 were withdrawn from vaccine (7 subjects in the aQIV group and 4 subjects in the comparator vaccine group).

Four of the 19 cases concerned unrelated AEs with the outcome of death (1 aQIV vs. 3 comparator group). Five of the 19 subjects experienced other SAEs of which 3 cases were related to study vaccine (all in the aQIV group). Of the remaining 10 non-serious cases, 7 were related to study vaccine (4 in the aQIV group and 3 in the comparator group). The 4 related non-serious cases in the aQIV group included peripheral swelling and rash (same subject), injection site pruritus, ILI, and hypersensitivity; the 3 related cases in the comparator group included sleep terror, injection site pain and ILI.

In general, numbers of AEs leading to withdrawal were evenly spread over multiple SOCs for both vaccine groups, except for the SOC Immune system disorders, where there were 4 subjects in the aQIV group

(1 subject with allergy to arthropod bite and 3 subjects with hypersensitivity events; all 4 were SAE cases), and none in the comparator group.

Pivotal Pooling

In the overall study population of the Pivotal Pooling, 25 of the 15,208 subjects (0.2%) experienced AEs that led to vaccine or study withdrawal with no statistically significant differences in risk between the vaccine groups. Of these, 23 subjects were vaccine naive and in 14 of them, the second vaccination was not administered (7 in each vaccine group). In 10 subjects (7 aQIV/aTIV, 3 QIV-1/TIV-1) the AEs were considered related to study vaccination by the investigator.

No increased risk was found for subjects with related AEs leading to vaccine or study withdrawal for aQIV/aTIV.

Supportive Pooling

In the Supportive Pooling study population, 6 of the 1099 subjects (0.1%) experienced AEs that led to vaccine or study withdrawal (2 [0.4%] aQIV/aTIV and 4 [0.7%] TIV group).

Revaccination Studies V118_05E1 and V118_05E3

In revaccination studies V118_05E1 and V118_05E3 none of the unsolicited AEs after study vaccination led to premature withdrawal from the study for any of the subjects.

Post marketing experience

There is limited paediatric post marketing experience with aTIV in children 6 months to <6 years (only approximately 4,000 doses of aTIV were distributed in Canada). Thus, since they are considered relevant post-marketing safety data from the adjuvanted pandemic vaccine aH1N1 (Focetria, Seqirus) that contains one of the four strains (A/H1N1) of influenza virus included in the aQIV formulation and is adjuvanted with MF59 have been submitted.

It is estimated that approximately 1.2 million doses of Focetria have been administered in children aged 6 months to <6 years following declaration of pandemic in 2009. The cumulative post marketing reports of important identified and potential risks listed in the Focetria Risk Management Plan up to the data lock point of 30 November 2018 are presented.

Overall, AEs relevant to the important identified or potential risks were reported in very small numbers in children 6 months to <6 years of age vaccinated with Focetria. Convulsion is the only event with a reporting frequency greater than 1 per 100,000 vaccinated children.

Eighteen reports of convulsion were retrieved and 8 of the 18 convulsion reports described febrile seizures (i.e., reporting rate of 0.67 per 100 000 doses). Overall, the majority of reports of convulsions described confounding factors, such as prior history of seizure or underlying condition associated with seizure activity, concurrent infections, and concomitant vaccination. No report was associated with neurologic sequelae following the convulsive episode. There was one case of febrile convulsions with a fatal outcome, and a brief summary of the case is described.

Case ID PHHY2010AR35307 concerned a 2.5-year-old child vaccinated with 2 doses of Focetria. The child has a history of febrile seizure following childhood immunizations and seasonal influenza vaccine.

On the same day after receipt of the second Focetria dose, the child developed fever and experienced a convulsive episode that lasted two hours. The patient was treated with diazepam and then with phenytoin. During the transfer to the hospital the child experienced a cardio-respiratory arrest that lasted for 15 minutes and lead to encephalic death. The child lived in a rural area with limited emergency

medical service. The fatal outcome seems to be primarily attributable to the lack of appropriate and timely medical assistance.

2.6.1. Discussion on clinical safety (paediatric indication)

In the initial submission, the Applicant sought a paediatric indication for children 6 to < 72 months of age. Following the responses of the D180 LoOI the Applicant tightened the age indication to children 6 to < 24 months of age. The paediatric indication was withdrawn by the Applicant within the responses of the 2nd D180 LoOI.

The total number of subjects 6 to <72 months of age exposed to aQIV in the pivotal study V118_05 was 5,339, this is above the 3,000 subjects recommended in the Guideline for Influenza Vaccines (EMA/CHMP/VWP/457259/2014), and constitutes an adequate safety database on itself. The study was performed in agreement with PIP EMEA-001715-PIP01-14-M01.

In addition, the applicant has submitted supportive data from clinical studies with Fluad, an adjuvanted trivalent influenza vaccine (aTIV), performed in children 6 to <72 months of age.

The safety database also includes two revaccination studies (V118_05E1 and V118_05E3) in which paediatric subjects that received aQIV in the pivotal study V118_05 were revaccinated with aQIV/QIV the following season.

Supportive data is included in two pooled safety analyses. In the pivotal pooling, safety data from the pivotal aQIV study V118_05 and the pivotal aTIV study V70_29 are included. The reason for this pooling is the safety evaluation of infrequent adverse events. However, in general the pooled results are considered of limited value as the comparator non-adjuvanted vaccines were different in the different studies.

Overall, 6,483 children were exposed to aQIV throughout the clinical studies, 3,647 children were exposed to the trivalent formulation aTIV and 7,692 to a comparator vaccine. The pivotal study in support of the paediatric indication included children at high risk of influenza due to underlying comorbidities. Children with compromised immune function were however excluded.

Solicited Adverse Events

The safety data from pivotal aQIV study V118_05 in subjects 6 to <72 months of age shows that the incidence of any solicited AEs is higher in subjects that were administered the aQIV vaccine compared to the non-adjuvanted vaccine after any vaccination (72.95% vs. 64.12%, respectively). The same pattern is also observed for any solicited local AEs, systemic AEs or other indicators of reactogenicity (use of antipyretics/analgesics).

The most frequently reported solicited local AEs in both vaccine groups in the 6 to <72 months of age population were tenderness and erythema. The proportion of subjects with any tenderness was higher in the aQIV group (43.19%) than in the comparator group (33.86%) and a slightly higher proportion of subjects experienced moderate or severe tenderness, erythema or induration after aQIV as compared to the comparator.

The most frequently reported solicited systemic AEs reported were irritability, sleepiness and change in eating habits in both aQIV and comparator vaccine groups.

The proportion of subjects with reported irritability, sleepiness and change in eating habits was slightly higher in aQIV than comparator vaccine. A low proportion of subjects reported severe irritability, sleepiness, and change in eating habits.

In the aQIV group a greater proportion of subjects experienced fever ≥38°C than in the comparator vaccine group (19.1% vs. 10.5%), fever ≥39.0°C to <40°C was also reported in a higher proportion in subjects in the aQIV group than in the comparator group (4.1% vs. 2.3%). A low percentage of subjects had body temperature ≥40°C, which was similar for both vaccine groups (0.4% aQIV, 0.3% comparator vaccine group). The therapeutic use of analgesics/antipyretics was higher with aQIV as well (aQIV: 29.89%; comparator: 17.94%).

Within vaccine naïve subjects, that received two doses of the vaccine, the proportion of subjects with any solicited local and systemic AE after vaccination 2 was higher for the aQIV group than for the comparator group.

Although infrequent, the number of subjects reporting moderate to severe solicited AEs was higher in the groups that received the aQIV vaccine.

In the two aQIV revaccination studies similar to the results obtained in pivotal aQIV study, reactogenicity (local and systemic) was consistently higher after vaccination with aQIV than with the comparator vaccine.

The applicant concluded that the observed increased reactogenicity is to be expected for an adjuvanted vaccine. Data from the three independent aQIV studies consistently demonstrates that the aQIV vaccine causes significantly more local and systemic adverse events than the non adjuvanted comparator vaccine in the paediatric population. Further, in pivotal study V118_05 the severity of practically all the local and systemic adverse events is higher in the recipients of the aQIV vaccine. The small differences in frequencies of moderate-to-severe solicited AEs, and the fact that the majority spontaneously resolved within 3 to 4 days, make these findings not clinically significant. This conclusion is not supported, and since an improved clinical efficacy of the aQIV vaccine has not been demonstrated this increased reactogenicity upholds the negative benefit risk balance of the aQIV vaccine for the paediatric population.

In revaccination study V118_05_E03 the proportion of subjects with solicited AEs, was higher with aQIV compared to QIV, regardless of the vaccine allocation (aQIV or non adjuvanted comparator) in the parent study. This increased proportion solicited AEs is more marked when the aQIV groups are combined. In this study the incidence of any solicited AE was clearly higher in subjects in the aQIV/aQIV group compared with the QIV/QIV group (64.76% vs. 40.71%).

Additionally, in this study 21.6% of subjects who received an aQIV two years in a row reported fever compared to 11.7% of subjects who received an aQIV after having received a non-adjuvanted vaccine in the year previous. In those who received a non-adjuvanted vaccine, the fever rate was approximately 7.5%. For other systemic reactions a similar pattern was seen, with higher rates in subjects who received aQIV two years in a row compared to those who received aQIV following a non-adjuvanted vaccine in the year previous. Although the majority of reactions were mild, this is a potential safety signal with implications for the B/R of annual revaccination with aQIV and required further investigation. The applicant points to inconsistency in fever rates between the revaccination studies (on different seasons) suggesting that the fever rates in study V118_05E3 might not be representative.

Although systemic reactions were mostly mild, an aQIV/aQIV regimen resulted in higher systemic reactogenicity as compared to an aQIV/QIV regimen but also as compared to an QIV/aQIV regimen. This may translate into an increased rate of more severe reactions to revaccination with aQIV as compared to initial vaccination with aQIV or revaccination with QIV following priming with aQIV, yet

this cannot be determined based on the available data. Nonetheless, an increase in reactogenicity of this magnitude could only be acceptable if there is clear evidence of an additional benefit. As this increased reactogenicity is not off set by a clear and consistent immunological benefit of revaccination with aQIV the B/R of annual revaccination with aQIV in children is considered negative.

Unsolicited AEs /SAEs

The proportion of unsolicited AEs in pivotal aQIV study V118_05 during the treatment period was similar for the aQIV and comparator groups (49.91% versus 50.05%). The most frequently reported unsolicited AEs included ILI, upper respiratory tract infection and nasopharyngitis.

The proportion of possibly related unsolicited AEs was slightly higher in the aQIV group than the comparator group during the treatment period (12.76% vs. 10.08%) as well as during the overall study period (13.08% for vs. 10.33%). The most frequently reported related AE during the treatment period was ILI.

In study V118_05 severe AEs were reported in a 4.46% for both vaccine groups. Possible/probably related SAEs according to the investigator were reported in 6 subjects in aQIV group and in 1 subject in comparator vaccine group.

In the Pivotal Pooling the proportion of subjects that experienced at least one SAE was similar in the adjuvanted and non-adjuvanted vaccine groups. One additional related SAE identified in the aTIV group was reported, therefore from the 8 SAEs related to the vaccine 7 was in the aQIV/aTIV group.

The majority of SAEs was reported in the SOC Infections and infestations. The most frequently reported PTs were pneumonia, animal bite, and gastroenteritis.

The applicant's conclusion is that an increased risk of related AEs or SAEs has not been identified for the aQIV vaccine since differences in risk ratios between aQIV/aTIV and QIV-1/TIV-1 groups were not statistically significant. This conclusion was not entirely supported. In response to the request to discuss of these findings the applicant confirmed that in study V118_05 the frequency of related unsolicited AEs was higher in the aQIV group than the comparator group (13.08% vs 10.33%) and that the proportion of possibly or probably related severe AEs was 0.11% in the aQIV group and 0.02% in the comparator group. The differences are confirmed but the small number of events recorded renders them inconclusive.

There were no vaccine-related deaths throughout the clinical studies.

AES leading to Withdrawal from Study Drug

In the pivotal study 19 subjects, reported AEs leading to premature withdrawal. Four cases were due to deaths that were unrelated to the vaccines. Five subjects experienced SAEs of which 3 cases were related to study vaccine (all in the aQIV group). Of the 10 non-serious AEs, 4 were related to study vaccine in the aQIV group and 3 in the comparator group. The 4 related non-serious cases in the aQIV group included peripheral swelling and rash (same subject), injection site pruritus, ILI, and hypersensitivity; the 3 related cases in the comparator group included sleep terror, injection site pain and ILI. In the SOC Immune system disorders, there were 4 SAE reported in the aQIV group and none in the comparator group, all cases were reported in study V118_05.

Only 6 more cases (25 in total) of AEs that led to vaccine or study withdrawal were reported in the pivotal pooling. Of these 7 AEs were considered related to vaccination by the investigator in the aQIV/aTIV group and 3 AEs in the QIV 1/TIV 1 group. Of the related AEs in the QIV-1/TIV-1 group "sleep terror" was considered to be an AE related to the vaccine and not to the vaccine "administration". However, the observed relative risk differences between aQIV/aTIV and comparator vaccines for related AEs leading to discontinuation was no statistically significant.

Adverse Events of Special Interest

In study V118_05, 9 AESIs were reported after vaccination: 5 AESIs in the aQIV group and 4 in the comparator group. In the Pivotal Pooling, the overall incidence of retrospectively identified AESIs was ≤0.2% in each vaccine group. Of the 12 cases reported, 7 were identified in the aQIV/aTIV group and 5 in the QIV-1/TIV-1 group. The identified AESIs in pivotal study V118_05, were unlikely to be causally related to the vaccine.

Five AESIs were reported after vaccination with aQIV (Henoch-Schönlein purpura, Crohn's disease, Type I diabetes mellitus, Kawasaki's disease and Encephalitis autoimmune) and four after vaccination with comparator vaccines in the pivotal studies (Type I diabetes mellitus, Henoch-Schönlein purpura, Immune thrombocytopenia and Coeliac Disease). In the revaccination studies an additional three AESIs were reported, one in the aQIV group (Immune thrombocytopenic purpura), and two in the QIV group (Type I diabetes mellitus and Kawasaki). The applicant indicated that none of these events were related to the vaccines. For a case of Kawasaki disease there was an error in the original CSR regarding the relation to the vaccine. This was corrected in the CSR addendum. The issue was considered resolved provided that future potential cases of Kawasaki's disease will be monitored via routine pharmacovigilance activities (including signal detection and the PSURs).

The pivotal pooling doesn't add any information as 11 of the 12 retrospectively identified AESIs were reported in the pivotal aQIV study (7 in aQIV, 4 QIV) and only 1 AESI (in the TIV group) was retrospectively found in supportive aTIV study.

Adverse Events Following Immunization (AEFIs)

Due to their low frequency AEFIs were analysed in the Pivotal Pooling which integrated data from pivotal study V118_05 with aQIV and aTIV supportive study V70_29.

In subjects 6 to <72 months of age AEFIs were identified in 20 subjects (0.2%) in the aQIV/aTIV group and 12 (0.2%) in the QIV-1/TIV-1 group. Of those the majority were included in the hypersensitivity category: 16 (0.2%) in the aQIV/aTIV group and 11 (0.2%) in the QIV-1/TIV-1 group.

Of the 8 SAEs reported in subjects aged 6 to <72 months in the aQIV/aTIV group considered by the study investigator to be at least possibly related to the study vaccine six cases were hypersensitivity type reactions. The assessment of the applicant, that "the nature and severity of these related hypersensitivity-like SAEs events did not raise any safety concerns with aQIV" it is not completely endorsed.

Although reactions were varied in timing in relation to vaccination and in appearance, there was an imbalanced reporting of serious hypersensitivity reactions following aQIV compared to comparator vaccines. This could be coincidental, however it cannot be excluded, based upon the available data, that vaccination with aQIV might increase the risk of hypersensitivity and this would indeed raise a safety concern. The listing of these reactions in the SmPC is acknowledged however further monitoring via routine pharmacovigilance is required.

The applicant was asked to address the increased number of hypersensitivity-like potentially related SAEs associated to the aQIV/aTIV vaccines, to review reports of hypersensitivity reactions with MF59 adjuvanted influenza vaccines, and to examine if there are potential factors that might predict the risk. Based upon the information provided by the applicant it is concluded that there is no evidence of an increased risk of anaphylactic reactions associated with MF59 adjuvanted pandemic influenza vaccine (A/H1N1pdm09) in children, neither is evidence of an increased risk of anaphylactic reactions associated with MF59 seasonal influenza vaccine in older adults. The applicant's plan to analyse hypersensitivity reactions including anaphylaxis in future PSURs is agreed.

Regarding febrile convulsions in subjects 6 to <72 months 4 cases (<0.1%) were reported in the aQIV/aTIV group and 1 case (<0.1%) in QIV-1/TIV-1 group. Three cases were considered possibly related to aQIV/aTIV, all occurred within a week of vaccination. Although there were factors for each case that could have contributed to the occurrence of the febrile convulsion, it cannot be excluded that vaccination with aQIV may have contributed as well. Moreover, from the pivotal pooling it appears that the risk is slightly higher following aQIV/aTIV (n=26, 0.3%) compared to QIV/TIV (n=10, 0.1%) with a RR of 1.85 (0.89-3.85). The risk ratios of febrile convulsions in the aQIV/aTIV group as compared to QIV-1/TIV-1 group did not reach statistical significance due to the low numbers reported. The applicant states that the reported febrile convulsions were temporally associated with the vaccination, but additional comorbidities were reported for 4 of the 5 cases and that it cannot be excluded their potential contribution to the incidence of febrile convulsion. As such, the applicant concludes it is not possible to attribute an increased risk for febrile convulsions, to the aQIV vaccine. The draft SmPC submitted as part of the initial dossier included Febrile convulsions as listed AE. Following withdrawal of the paediatric indication, the agreed SmPC does not include febrile convulsion.

As requested the applicant provided new tables in which infrequent events, if there were events recorded, the percentages were displayed as <0.1% rather than 0.0%.

New Onset of Chronic Disease

In study V118_05, the proportion of subjects reporting unsolicited AEs leading to NOCD as assessed by the investigator was similar for the aQIV group and comparator vaccine groups (<2%). The most frequently reported NOCDs during the overall period were asthma, seasonal allergy and attention deficit/hyperactivity disorder. The incidence of theses NOCDs was similar in both vaccine groups. Overall, the nature and frequency of these clinical symptoms that are reported as NOCDs does not constitute a risk associated with aQIV/aTIV.

Subjects at high risk of influenza complications

In Study V118_05, an 8.7% of the subjects were considered to be at high risk of influenza complications (aQIV: 8.8%, comparator vaccine group: 8.6%). No difference apparent was observed in the group of subjects at high risk of influenza complications.

Age, Race etc.

The impact of age on the rate of solicited adverse events is variable dependent on the type of solicited AE and there is no overall pattern of a relative increase in solicited adverse events in younger children. The fever rates are similar over all age groups in the aQIV recipients, ranging from 17.8% and 20.3%, whilst the rates increase with decreasing age in the non-adjuvanted vaccine group.

Safety data for males and females was similar for both vaccine groups.

The safety of the aQIV or the aTIV vaccines in immunocompromised subjects 6 to <72 months of age has not been studied.

No safety data related to the interaction of aQIV or aTIV vaccines with other vaccines administered to children 6 to 72 months of age has been provided. The reactogenicity of the aQIV vaccine could be further increased when co-administered with other vaccines, this should be clearly indicated in the SmPC.

Post-marketing studies

Only approximately 4000 doses of the trivalent adjuvanted vaccine Fluad have been administered in children 6 months to <6 years of age, authorized in Canada. As supportive data the applicant has presented the post-marketing safety data from the adjuvanted pandemic vaccine aH1N1 Focetria that contains one of the four strains (A/H1N1) of influenza virus included in the aQIV formulation and is

adjuvanted with MF59. Approximately 1.2 million doses of Focetria were administered in children aged 6 months to <6 years in 2009. The results show that convulsion is the most commonly reported AE and the only event with a reporting frequency greater than 1 per 100,000 vaccinated children. These results are consistent with the findings reported in the aQIV of clinical trials in which a higher proportion of febrile convulsions have been identified in the aQIV group than in the comparator vaccine. In one of the reported Focetria cases a 2.5 year old child after receipt of the second Focetria dose developed fever and experienced a long lasting convulsive episode that lead to death. The applicant agrees that postvaccination reaction and febrile convulsion will be events of interest requiring close monitoring in a postmarketing setting, although no specific safety concern has been observed to date. It is planning to conduct monitoring for the occurrence of febrile convulsion through routine postmarketing surveillance complemented by enhanced safety surveillance (EMA/PRAC/222346/2014).

2.6.2. Conclusions on the clinical safety (paediatric indication)

The safety data from the three independent aQIV studies consistently demonstrates that in children >6 to <72 months the aQIV vaccine causes more local and systemic adverse events that the non-adjuvanted comparator vaccine. Of note high fever is more frequent in children that received the aQIV vaccine. Further, the severity of the local and systemic adverse events tends to be higher in the recipients of the aQIV vaccine.

In addition, the differences in reactogenicity between the aQIV group and the comparator group are amplified when the aQIV vaccine is administered the following season. A potential signal of increased reactions in subjects who received aQIV in two subsequent years is of concern. As this increased reactogenicity is not offset by a clear and consistent immunological benefit of revaccination with aQIV, the B/R of annual revaccination with aQIV in children is considered negative.

When looking at total number of cases, although not statistically significant, an increase risk of unsolicited AEs and SAEs related to the vaccine, for example hypersensitivity reactions and febrile convulsions, is observed in children vaccinated with the aQIV vaccine in comparison with those that received the non-adjuvanted QIV vaccine. However, these reactions occur very rarely (<0.1%).

Since a superior clinical efficacy of the aQIV vaccine against influenza infection has not been demonstrated the increase in proportion and severity of local and systemic solicited adverse events associated to the administration of aQIV upholds the negative benefit risk balance of the aQIV vaccine for the paediatric population.

2.7. Clinical safety (elderly indication)

Patient exposure

The Phase III pivotal study, V118_20, comparing aQIV versus the adjuvanted trivalent influenza vaccines (aTIV-1, Fluad) and aTIV-2 (containing the alternate B strain), enrolled 1,778 subjects, of which 888 were exposed to aQIV, 444 subjects to aTIV-1 and 444 subjects to aTIV-2.

Overall, 6,790 subjects were enrolled in the Phase III study, V118_18. Of these, 6,761 subjects were exposed to study treatment with a similar number of subjects exposed to aQIV and non- influenza comparator, Boostrix (3381 received aQIV and 3380 received Boostrix). Most enrolled subjects (96.3%) completed the study.

For the safety evaluation, a subset of 1,332 subjects had solicited safety assessments beyond 30 minutes and were included in the Solicited Safety Set. Overall, 6,757 exposed subjects provided unsolicited safety data and were included in the Unsolicited Safety Set.

Therefore, the study V118_18 provides additional safety data and contributes to increase the safety database including 665 subjects ≥ 65 years of age exposed to aQIV to be assessed for the solicited safety subset, and 3,380 subjects for the assessment of Unsolicited AEs, SAEs and deaths, NOCDs, and AESI. The proportion of subjects included in the safety analysis sets was similar between aQIV and non-influenza vaccine comparator Boostrix.

The study V70_27, comparing aTIV versus the registered non-adjuvanted TIV (Agriflu) enrolled 7,109 subjects, of which 7,082 were exposed to the study vaccines, being 3,545 exposed to aTIV (Fluad) and 3,537 to TIV (Agriflu).

Safety data from revaccination studies with aTIV were pooled by year of vaccination and included all the subjects who had received the vaccination in Year 1. Subjects from Year 1 were invited to participate in an annual revaccination study for 2 (Year 2) or 3 (Year 3) consecutive seasons and received the same vaccine upon revaccination.

1,214 subjects included in studies V7P3, V7P5, V7P7, V7P8, V7P25 received Vaccination 1 (Year 1). 822 of them were included in the respective extension studies (V7P3X1, V7P5X1, V7P7X1, V7P8X1, V7P25X1) for Year 2. 237 of them received the third vaccination (Year 3: V7P3X2, V7P5X2). The number of subjects exposed to aTIV or TIV in Years 1, 2 or 3 are summarized in the Table below.

Table 59: aTIV Revaccination Pooling, Number of Subjects Exposed by Vaccination

Vaccination by Year	aTIV	TIV	Total
Vaccination 1	713	501	1214
Vaccination 2	492	330	822
Vaccination 3	150	87	237

Source: Appendix A, Table 2.1.3.1, Table 2.1.2.1.1, and Table 2.1.2.1.2
Abbreviations: aTIV = Adjuvanted Trivalent Influenza Vaccine; TIV = Trivalent Influenza Vaccine

Table 61 provides a summary of subjects included in the clinical safety database by vaccine group: aQIV, aTIV (aTIV-1), aTIV-2 and TIV. Overall, 4,269 subjects were exposed to aQIV; and 5,146 subjects were exposed aTIV (aTIV-1) and aTIV-2.

Table 60: Overall Extent of Exposure

Study	aQIV	aTIV (aTIV-1)	aTIV-2	TIV	Total
	N = 4269	N = 4702	N = 444	N = 4038	N = 13453
Pivotal aQIV studies and key supportive aTIV study					
V118_20	888	444	444	N/A	1776
V118_18	3381	N/A	N/A	N/A	3381
V70_27	N/A	3545	N/A	3537	7082
Year 1 aTIV Revaccination Pooling					
V7P3	N/A	46	N/A	46	92
V7P5	N/A	212	N/A	105	316
V7P7	N/A	109	N/A	105	214
V7P8	N/A	204	N/A	104	308
V7P25	N/A	142	N/A	141	283
Year 2 aTIV Revaccination Pooling					
V7P3X1	N/A	39	N/A	35	74
V7P5X1	N/A	143	N/A	73	216
V7P7X1	N/A	75	N/A	64	139
V7P8X1	N/A	148	N/A	69	217
V7P25X1	N/A	87	N/A	89	176
Year 3 aTIV Revaccination Pooling					
V70P3X2	N/A	35	N/A	32	67
V70P5X2	N/A	115	N/A	55	170

Source: CSR V118_20; CSR V118_18; CSR V70_27; CSR V7P3; CSR V7P5; CSR V7P7; CSR V7P8; CSR V7P25; CSR V7P3X1; CSR V7P5X1; CSR V7P7X1; CSR V7P8X1; CSR V7P25X1; CSR V7P3X2; CSR V7P5X2
Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; aTIV = adjuvanted Trivalent Influenza Vaccine; N/A = not applicable; TIV = trivalent influenza vaccine

Demographics and Other Characteristics of Study Population

Demographic and baseline characteristics data for studies V118_20, V118_18 and V70_27 are presented individually. For the 12 supportive aTIV studies included in the revaccination pooling, demographic and baseline characteristics data are presented as an integrated summary.

Study V118_20

Demography

There were no notable differences observed in the baseline characteristics and demographics across vaccine groups in the overall enrolled population. The median age was 71 years overall with a minimum age of 65 years, and a maximum age of 97 years.

Study V118_20 was conducted in the US. The majority of the enrolled subjects were female (56.6%) and predominantly white (91.6%) and non-hispanic (92.5%). The majority of subjects (68.8%) were 65 to 74 years of age and only 3.3% of all subjects were ≥85 years of age.

Table 61: Study V118_20, Summary of Demographics and Baseline Characteristics – All Enrolled Set

	aQIV N = 889	aTIV-1 N = 445	aTIV-2 N = 444	Total N = 1778
Age (years)				
Mean	72.4	72.4	72.6	72.5
Median (Min, Max)	71.0 (65, 97)	71.0 (65, 92)	72.0 (65, 90)	71.0 (65, 97)
Age group, n				
65 to 74 years	612	311	297	1220
75 to 84 years	246	120	133	499
≥85 years	31	14	14	59
Total Risk Score (Comorbidity)				
Mean	46.0	44.6	46.5	45.8
BMI				
Mean	29.60	29.79	29.69	29.67
Median (Min, Max)	28.62 (16.9, 64.4)	28.96 (14.8, 58.2)	28.93 (18.0, 57.7)	28.86 (14.8, 64.4)
Gender, n (%)				
Male	372 (41.8)	196 (44.0)	203 (45.7)	771 (43.4)
Female	517 (58.2)	249 (56.0)	241 (54.3)	1007 (56.6)
Race, n (%)				
White	814 (91.6)	403 (90.6)	411 (92.6)	1628 (91.6)
Black or African American	59 (6.6)	37 (8.3)	29 (6.5)	125 (7.0)
Asian	9 (1.0)	2 (0.4)	1 (0.2)	12 (0.7)
Native Hawaiian or Pacific Islander	1 (0.1)	1 (0.2)	0	2 (0.1)
American Indian or Alaska Native	5 (0.6)	0	2 (0.5)	7 (0.4)
Other	1 (0.1)	2 (0.4)	1 (0.2)	4 (0.2)
Ethnicity, n (%)				
Hispanic or Latino	59 (6.6)	37 (8.3)	31 (7.0)	127 (7.1)
Not Hispanic or Latino	827 (93.0)	408 (91.7)	410 (92.3)	1645 (92.5)
Not Reported	2 (0.2)	0	2 (0.5)	4 (0.2)
Unknown	1 (0.1)	0	1 (0.2)	2 (0.1)
Influenza Vaccination History, n (%)				
Yes	760 (85.5)	380 (85.4)	401 (90.3)	1541 (86.7)

Source: CSR V118_20, Table 14.1.1.3.1
Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; aTIV = adjuvanted Trivalent Influenza Vaccine; BMI = body mass index; Max = maximum; Min = minimum
Notes:
aTIV-1 used in study V118_20, contains strains recommended by the WHO for trivalent vaccines; aTIV-2 contains the 2 A strains recommended by WHO for trivalent vaccines and the alternate B strain
Subjects who refused to identify their ethnicity were coded as not reported. Subjects who did not know their ethnic background were coded as unknown

Medical History

The 97.7% subjects had at least 1 disorder recorded in their medical history. Prior medical disorders were reported in similar proportions of subjects across vaccine groups (aQIV 97.8%, aTIV-1 97.3%, aTIV-2 98%).

The most common disorders in medical histories were vascular disorders 63.0%; metabolism and nutrition disorders 59.4%; musculoskeletal and connective tissue disorders 54.6%; immune system disorders 42.4%; gastrointestinal disorders 40.5%; and eye disorders 37.8%.

Concomitant Use of Medications

From the 1778 (100%) subjects enrolled in the study no major differences were seen between vaccine groups. However, the aTIV-1 group had a higher average number of subjects taking medications compared to the aQIV and aTIV-2 vaccine groups.

The frequency of medications used was generally similar across groups.

Study V118_18

Demography

Study V118_18 was conducted in total at 89 sites in 12 countries. Overall, the demographic and baseline characteristics of subjects enrolled in this study were well balanced between the two vaccine groups with similar age, sex, ethnicity, race, and BMI. The mean age was 71.9 years and 71% of subjects were in the 65-74 year age group.

More than half of the subjects were female (61.8%). The majority of subjects were either White (48.2%) or Asian (33.8%).

Table 62: Study V118_18, Summary of Demographic and Baseline Characteristics - All Enrolled Set

	aQIV N = 3394	Boostrix N = 3396	Total N = 6790
Age (Years)			
Mean (SD)	71.9 (5.53)	71.8 (5.36)	71.9 (5.44)
Median	71.0	71.0	71.0
Age Group, n (%)			
65 to 74 years	2416 (71.2)	2406 (70.8)	4822 (71.0)
75 to 84 years	893 (26.3)	928 (27.3)	1821 (26.8)
≥ 85 years	85 (2.5)	62 (1.8)	147 (2.2)
Total Risk Score (Comorbidity), n (%)			
< 50	2472 (72.8)	2474 (72.9)	4946 (72.8)
≥ 50	922 (27.2)	922 (27.1)	1844 (27.2)
BMI			
Mean (SD)	27.05 (4.989)	26.96 (4.995)	27.00 (4.992)
Median	26.60	26.50	26.50
Gender, n (%)			
Male	1289 (38.0)	1307 (38.5)	2596 (38.2)
Female	2105 (62.0)	2089 (61.5)	4194 (61.8)
Race, n (%)			
White	1642 (48.4)	1629 (48.0)	3271 (48.2)
Black or African American	1 (0.0)	0	1 (0.0%)

	aQIV N = 3394	Boostrix N = 3396	Total N = 6790
Asian	1139 (33.6)	1159 (34.1)	2298 (33.8)
Native Hawaiian or Pacific Islander	0	0	0
American Indian or Alaska Native	62 (1.8)	59 (1.7)	121 (1.8)
Other	550 (16.2)	549 (16.2)	1099 (16.2)
Ethnic Origin, n (%)			
Hispanic or Latino	615 (18.1)	607 (17.9)	1222 (18.0)
Not Hispanic or Latino	2773 (81.7)	2779 (81.8)	5552 (81.8)
Not Reported	5 (0.1)	10 (0.3)	15 (0.2)
Unknown	1 (0.0)	0	1 (0.0)
Influenza Vaccination History, n (%)			
Yes	991 (29.2)	1021 (30.1)	2012 (29.6)

Source: CSR V118_18, Table 14.1.1.3
Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; BMI = body mass index; Max = maximum; Min = minimum; SD = standard deviation
Notes:
Percentages are based on the number of subjects in each vaccine group.
Influenza vaccination history collected for past 5 years.

Medical History

All the subjects enrolled were healthy or had co-morbidities. At least one medical disorder in medical history was reported for 6151 (90.6%) subjects; the percentages of subjects with medical disorders were similar in the two vaccine groups. Twenty seven percent (27.2%) of subjects had a comorbidity score ≥ 50. Most of the subjects were non-smokers (90.3%).

Concomitant Use of Medications

All subjects in aQIV and Boostrix groups used at least one concomitant medication. Of these, 41.2% and 39.4% of subjects in the aQIV and Boostrix groups, respectively, received at least one unique medication. The concomitant medications taken were generally similar across both vaccine groups.

A higher number of subjects had not received a seasonal influenza vaccine in the past 5 years (70.4%).

Study V70_27

Demography

There were no differences observed in the baseline characteristics and demographics across vaccine groups in the overall enrolled population.

Study V70_27 was conducted in the Philippines, US, Colombia, and Panama. The majority of the enrolled subjects were female (65%) and predominantly Asian (53%) and White (28%).

The median age was 71 years overall with a minimum age of 65 years, and a maximum age of 97 years. The study was stratified in two age groups (65 to 74 years and 75 to 84 years), as seen in Table 1-6).The majority of subjects (72%) were 65 to 74 years of age.

Table 63: Study V70_27, Summary of Demographics and Baseline Characteristics – Safety Set

	aTIV N = 3545	TIV N = 3537	Total N = 7082
Age (years)			
Mean	72.0	71.8	71.9
Median (Min, Max)	72.0 (65, 97)	71.0 (65, 95)	71.0 (65, 97)
Age group, n (%)			
65 to 75 years	2545 (72)	2570 (73)	5115 (72)
>75years	1000 (28)	967 (27)	1967 (28)
BMI			
Mean	25.32	25.40	25.36
Median (Min, Max)	24.80 (12.6, 60.8)	24.80 (11.2, 53.3)	24.80 (11.2, 60.8)
Gender, n (%)			
Male	1273 (36)	1195 (34)	2468 (35)
Female	2272 (64)	2342 (66)	4614 (65)
Race/Ethnicity, n (%)			
White	974 (27)	974 (28)	1948 (28)
Black or African American	44 (1)	39 (1)	83 (1)
Asian	1880 (53)	1875 (53)	3755 (53)
Native Hawaiian or Pacific Islander	1 (<1)	3 (<1)	4 (<1)
American Indian or Alaska Native	1 (<1)	0	1 (<1)
Hispanic	634 (18)	630 (18)	1264 (18)
Other	11 (<1)	16 (<1)	27 (<1)
Country, n (%)			
Columbia	520 (15)	508 (14)	1028 (15)
Panama	109 (3)	105 (3)	214 (3)
Philippines	1875 (53)	1865 (53)	3740 (53)
United States	1041 (29)	1059 (30)	2100 (30)

Source: CSR V70_27, Table 14.1.1.3
Abbreviations: aTIV = adjuvanted Trivalent Influenza Vaccine; BMI = body mass index; Max = maximum; Min = minimum; TIV = Trivalent Influenza Vaccine

Medical History

The medical history conditions were similar between vaccine groups (i.e., within 1-2%). The most frequently reported medical history conditions in the total subject population were essential hypertension (55%), disorders of lipid metabolism (26%) and other postsurgical states (25%).

Concomitant Use of Medications

The majority of subjects in both vaccine groups in study V70_27 reported use of one or more concomitant medications (73% of subjects). Percentages of subjects receiving each of these concomitant medications were similar between vaccine groups.

aTIV Revaccination Pooling

Demography

Demographic and baseline characteristics for the 7 supportive revaccination studies (Year 2/Vaccination 2 and Year 3/Vaccination 3) reflect data collected in the parent study (Year 1/Vaccination 1). Demographic data were not recollected for the revaccination years.

Demographic and baseline characteristics for the aTIV revaccination pooling are presented by vaccine group in the Table below.

Table 64 Primary Studies, aTIV Revaccination Pooling, Summary of Demographics and Baseline Characteristics – All Enrolled Set

	aTIV N = 713	**TIV N = 501**
Age (years)		
Mean	76.8	77.7
Median (Min, Max)	77.0 (64, 97)	78.0 (64, 100)
Age group, n (%)		
50 to <65	6 (0.8)	1 (0.2)
65 to <75 years	312 (43.8)	194 (38.7)
75 to <85 years	276 (38.7)	200 (39.9)
≥85 years	119 (16.6)	106 (21.2)
BMI		
Mean	25.73	25.75
Median (Min, Max)	25.36 (14.9, 48.4)	25.39 (34.0, 110.0)
Gender, n (%)		
Male	293 (41.1)	200 (39.9)
Female	420 (58.9)	301 (60.1)
Race, n (%)		
White	706 (99.0)	496 (99.0)
Black or African American	2 (0.3)	1 (0.2)
Asian	4 (0.6)	4 (0.8)
Other	1 (0.1)	0

Source: Appendix A, Table 2.1.3.1
Abbreviations: aTIV = adjuvanted Trivalent Influenza Vaccine; BMI = Body Mass Index; Max = maximum; Min = minimum; TIV = Trivalent Influenza Vaccine

Medical History

A summary of medical history by SOC and PT for the 5 primary and 7 revaccination studies included in the aTIV revaccination pooling is provided in the individual study reports

Concomitant Use of Medications

The most frequently reported concomitant medications upon revaccination were generally similar to the most frequently reported medications at baseline.

Adverse events

The collection of safety data in clinical studies with aQIV and aTIV included an evaluation of solicited and unsolicited adverse events (AEs), AEs leading to study withdrawal, Serious AEs (SAEs), AEs of special interest (AESIs), and new onset chronic diseases (NOCDs).

Solicited AEs: Solicited AEs were predefined and were categorized as local AEs, systemic AEs and any use of antipyretics/analgesic for prevention or treatment of pain and/or fever.

In studies V118_20, V118_18 and V70_27, solicited AEs were recorded at approximately 30 minutes after vaccination and then daily from 6 hours following vaccination until Day 7. Solicited local and systemic AEs reported within 7 days of vaccination were considered as related to vaccination and therefore are reported as adverse reactions.

Unsolicited AEs**:** All unsolicited AEs were collected for 3 weeks (Day 1 to Day 22) after vaccination in studies V118_20, V118_18 and V70_27. Solicited AEs that were ongoing at 4 or 7 days after vaccination were to be recorded as unsolicited AEs. Unsolicited AEs were followed until resolution. The severity and the relationship to the study vaccine were determined by the investigator.

In addition, AESIs (for study V118_20 and V118_18) and NOCDs (for studies V118_20, V118_18 and V70_27) were collected prospectively during the overall study period. SAE, AEs leading to withdrawal, AESIs and AEs leading to NOCD were collected for a 6 month period in study V118_20 and a 12 month period in study V118_18 and V70_27.

The applicant has submitted the list of events considered AESIs for study V118_20.

An overview of AEs for studies V118_20, V118_18, and V70_27 is provided below in Table 66.

Table 65: Studies V118_20, V118_18, and V70_27, Overview of Adverse Events

	V118_20			V118_18		V70_27	
Adverse Event Type	**aQIV**	**aTIV-1**	**aTIV-2**	**aQIV**	**Boostrix**	**aTIV**	**TIV**
Solicited AE	**N = 833 n (%)**	**N = 439 n (%)**	**N = 438 n (%)**	**N = 665 n (%)**	**N = 667 n (%)**	**N = 3505 n (%)**	**N = 3495 n (%)**
Any solicited AE	457 (51.8)	214 (48.7)	211 (48.2)	228 (34.3)	215 (32.2)	1619 (46)	1164 (33)
Any solicited local AE	385 (43.6)	170 (38.7)	167 (38.1)	162 (24.4)	131 (19.6)	1137 (32)	593 (17)
Any solicited systemic AE	231 (26.2)	107 (24.4)	110 (25.1)	128 (19.2)	109 (16.3)	1120 (32)	902 (26)
Other indicators of reactogenicity	48 (5.4)	12 (2.7)	17 (3.9)	41 (6.2)	26 (3.9)	210 (6)	165 (5)
Unsolicited AE	**N = 888 n (%)**	**N = 444 n (%)**	**N = 444 n (%)**	**N = 3380 n (%)**	**N = 3377 n (%)**	**N = 3545 n (%)**	**N = 3537 n (%)**
Any unsolicited AE, Days 1-22	136 (15.3)	50 (11.3)	68 (15.3)	727 (21.5)	716 (21.2)	551 (16)	570 (16)
Any related unsolicited AE, Days 1-22	39 (4.4)	17 (3.8)	19 (4.3)	303 (9)	261 (7.7)	154 (4)	172 (5)
Any SAE	37 (4.2)	28 (6.3)	18 (4.1)	238 (7.0)	234 (6.9)	264 (7)	243 (7)
Related SAE	0	0	0	1 (0.0)	1 (0.0)	1 (<1)	3 (<1)
AESI	1 (0.1)	1 (0.2)	0	4 (0.1)	6 (0.2)	N/A	N/A
AE leading to death	2 (0.2)	0	0	33 (1.0)	34 (1.0)	52 (1)	46 (1)
AE leading to NOCD	23 (2.6)	16 (3.6)	14 (3.2)	321 (9.5)	305 (9.0)	227 (6)	223 (6)
AE leading to withdrawal	0	0	0	37 (1.1)	36 (1.1)	52 (1)	49 (1)

Source: CSR V118_20 Table 21 and Table 22; CSR V118_18, Table 37 and Table 38; CSR V70_27 Table 12.2.1.1-1, and Table 12.2.1.2-1.
Abbreviation: AE = adverse event; AESI = adverse event of special interest; aQIV = Adjuvanted Quadrivalent Influenza Vaccine; aTIV = Adjuvanted Trivalent Influenza Vaccine; CSR = clinical study report; NOCD = new onset of chronic disease; SAE = serious adverse event; TIV = Trivalent Influenza Vaccine; WHO = World Health Organization
Notes:
aTIV-1 used in study V118_20, contains strains recommended by the WHO for trivalent vaccines; aTIV-2 contains the 2 A strains recommended by WHO for trivalent vaccines and the alternate B strain as explained.
Related category included Possibly Related, and Probably Related. Related refers to those events that were related to the study vaccination, or with an unknown relationship. All solicited AEs were defined as related AEs.
For percentage, 0.0% is equivalent to < 0.01%. Only 0% represents true 0%.
Percentages are based on the number of subjects in each vaccine group.
In study V70_27, AESIs were not collected prospectively.

Solicited Adverse Events

Study V118_20

The percentage of subjects with any solicited AE reported from Day 1 to Day 7 after vaccination was 51.8% in the aQIV group, 48.7% in the aTIV-1 group, and 48.2% in the aTIV-2 group.

At least 1 local solicited local AE (43.6%, 38.7% and 38.1% in the aQIV, aTIV-1, and aTIV-2 groups, respectively), and at least 1 solicited systemic AE (26.2%, 24.4% and 25.1% in the aQIV, aTIV-1, and aTIV-2 groups, respectively) were reported by a slightly higher percentage of subjects receiving aQIV than those who received the aTIV comparators.

The most commonly reported local solicited AEs were any injection site pain (31.9%,28.1% and 25.5% in the aQIV, aTIV-1, and aTIV-2 groups, respectively), followed by erythema (7.6%, 7.4%, and 8.6% in the aQIV, aTIV-1, and aTIV-2 groups, respectively) and induration (7%, 5.4%, and 5.3% in the aQIV, aTIV-1, and aTIV-2 groups, respectively).

The most commonly reported systemic solicited AEs were fatigue (16.0% 15.4% and 11.6% in the aQIV, aTIV-1, and aTIV-2 groups, respectively), headache (12.0%, 10.6% and 11.3% in the aQIV, aTIV-1, and aTIV-2 groups, respectively), and arthralgia (9.1%, 8.5% and 7.1% in the aQIV, aTIV-1, and aTIV-2 groups, respectively).

Most solicited reactions (local and systemic) were reported as mild to moderate in severity. Few severe solicited AEs were reported in any group, being all of them below 1%, except for fatigue in the comparator aTIV-2 (1.4%).

Analgesics and/or antipyretics for prevention or treatment of pain and/or fever were taken by 5.4% of the subjects in the aQIV group versus 2.7 to 3.9% of the subjects in both aTIV comparator groups.

Study V118_18

Subjects who were vaccinated with a single dose of aQIV or non-influenza comparator on Day 1 were observed for at least 30 minutes post vaccination on Day 1 for any immediate reactions.

A subset of randomly selected subjects (1053 per vaccine group, assuming a 5% drop-out rate) were chosen to participate in a solicited safety subset. They were asked to fill out the Subject Diary cards from Day 1 to 7. Data from 665 and 667 subjects receiving aQIV and Boostrix respectively were obtained to assess the solicited adverse events.

The percentage of subjects with any solicited AE reported from Day 1 (6 hours) through Day 7 after vaccination was 34.3% in the aQIV group and 32.2% in the Boostrix group.

The proportions of subjects with local and systemic AEs were slightly higher in the aQIV group compared to the Boostrix group (24.4% vs. 19.6% for local reactions, and 19.2% vs. 16.3% for systemic reactions, respectively, see table 2-1 from 2.4.7 Summary of clinical safety).

The majority of local AEs were of mild or moderate intensity. The frequency of severe solicited AEs was low and similar in both vaccine groups (0 to 0.5% for local reactions in both vaccine groups, and 0% to 1.1% for aQIV and 0.2% to 0.6% for Boostrix for systemic reactions).

The most common local solicited AE was injection site pain, (16.3% and 11.2% in the aQIV and Boostrix groups, respectively), followed by erythema (10.8% and 10.5% in the aQIV and Boostrix groups, respectively) and induration (10.3 and 7.9% % in the aQIV and Boostrix groups, respectively).

The most commonly reported systemic solicited AEs were headache (10.8% and 8.3% in the aQIV, and Boostrix groups, respectively), fatigue (10.5% and 8.8% in the aQIV and Boostrix groups, respectively), and myalgia (7.7 and 6.1% in the aQIV and Boostrix groups, respectively).

Other indicators of reactogenicity, defined as use of antipyretics/analgesic for prevention of pain and/or fever within 7 days after vaccination was reported by 4.7% and 2.5% subjects in the aQIV and Boostrix groups, respectively. Overall, 3.8% and 2.8% of subjects in the aQIV and Boostrix vaccine groups used antipyretics/analgesics for treatment of pain and/or fever, respectively.

Study V70_27

The incidence of solicited AEs was higher in the aTIV group (46%) compared to the TIV group (33%).

At least 1 local solicited local AEs (aTIV, 32% versus TIV, 17%), and at least 1 solicited systemic AEs (aTIV, 32% versus TIV, 26%) were reported by a higher percentage of subjects receiving aTIV than those who received the TIV. See table 2-4 and 2-5 from 2.4.7 Summary of Clinical Safety.

The most commonly reported local solicited AEs were any injection site pain (aTIV, 29% versus TIV 12%) followed by tenderness (21%, and 11% in the aTIV and TIV respectively). Erythema, induration, and swelling (>25 mm in diameter) were reported by ≤1% of subjects in both groups during that period

The most commonly reported systemic solicited AEs were myalgia (15% and 10% in the aTIV and TIV groups, respectively), headache (13% and 11% in the aTIV and TIV groups, respectively), and fatigue (13% and 10% in the aTIV and TIV groups, respectively). Overall the incidence of fever was comparable between aTIV and TIV (3.6 % versus 3.4%). Most solicited reactions (local and systemic) were mild to moderate in severity. There were a few severe solicited AE in any group, all of them were reported to be ≤1%, severe fever (⩾40°C) was noted in 3 subjects (0.3%) in the aTIV group and 0 subjects in the TIV group. Most of the solicited local reactions were resolved by day 4 and were of mild or moderate intensity.

Furthermore, the use of analgesics/antipyretics (5% versus 4%) was low and similar between the aTIV and TIV groups, respectively.

Unsolicited Adverse Events

Study V118_20

In study V118_20, there were no notable imbalances in the percentages of subjects reporting unsolicited AEs in the aQIV, aTIV-1 and aTIV-2 vaccine groups.

At least 1 unsolicited AE was reported during the entire study period by 19.8% of subjects in the aQIV group .The most commonly reported AE (≥1%) by preferred term (PT) were influenza-like-illness (aQIV, 2% versus aTIV-1, 2.7% versus aTIV-2, 2.9%), injection site bruising (aQIV, 1.1% versus aTIV-1, 1.4% versus aTIV-2, 1.4%), injection site erythema (aQIV, 0.7% versus aTIV-1, 0.9% versus aTIV-2, 1.1%), upper respiratory tract infection (aQIV, 0.7% versus aTIV-1, 0.9% versus aTIV-2, 1.1%) and headache (aQIV, 0.6% versus aTIV-1, 0.7% versus aTIV-2, 1.8%). The percentage of subjects with possibly related unsolicited AEs were comparable across the vaccine groups (aQIV, 4.4% aTIV-1, 3.8% versus aTIV-2, 4.3%). In the aQIV group, unsolicited AEs considered possibly related to treatment included injection site bruising (1.0%), injection site erythema (0.7%), injection site induration (0.5%), injection site pruritus (0.5%), fatigue (0.3%) arthralgia (0.3%), myalgia (0.2%), headache (0.2%), and diarrhoea (0.3%).

Study V118_18

For all subjects, any unsolicited AE and concomitant medication use, after vaccination from Day 1 to Day 22 were collected. The percentage of subjects having unsolicited AEs was calculated from 3380 and 3377 subjects exposed to aQIV and Boostrix respectively.

The proportion of subjects with unsolicited AEs during the treatment period was similar between the vaccine groups (21.5% in aQIV group and 21.2% in Boostrix group). Most of them were reported as mild or moderate in severity. The proportion of subjects with unsolicited AEs that were assessed as related to the study vaccine were similar, although slightly higher in aQIV vs the Boostrix group (9.0% vs 7.7%, respectively, see Table 38).

The most frequently reported unsolicited AEs by System Organ Class (SOC) in the aQIV and Boostrix groups were General disorders and administration site conditions (10.7% and 9.7%, respectively); Respiratory, thoracic and mediastinal disorders (4.7% and 3.4%, respectively) and Infections and infestations (3.6% and 3.4%, respectively)

The most frequently reported unsolicited AE by Preferred Term (PT) in the aQIV and Boostrix groups was ILI (4.6%).

Study V70_27

In study V70_27, At least one unsolicited AE was reported by 16% of the subjects in both groups. See table 2-7 from 2.4.7 Summary of Clinical Safety).

The most commonly reported AES (≥1%) by preferred term were nasopharyngitis (aTIV, 2% versus TIV, 2%), headache (1% versus 2%), cough (1% per group), upper respiratory tract infection (1% per group), and dizziness (1% per group). All other AEs had a frequency of <1%. The percentage of subjects with possibly related unsolicited AEs were comparable across the vaccine groups (aTIV, 4% versus TIV, 5%).

Serious adverse event/deaths/other significant events

In study V118_20, subjects were followed for SAEs from Day 1 to Day 181 following vaccination. In study V118_18 and V70_27, subjects were followed for SAEs through Day 366 following vaccination.

Study V118_20

Deaths

A total of 2 subjects experienced SAEs with outcomes of death. Both deaths occurred in the aQIV group. The first case occurred 115 days after vaccination (08-02-2018), the second had an unknown onset day however was reported to occur in 01-2018. Both cases were considered not related to the study vaccine.

Other Serious Adverse Events

Overall, 83 (4.7%) subjects had at least 1 SAE during the study (4.2% of subjects in the aQIV group, 6.3% in aTIV-1 group and 4.1% in aTIV-2 group). In total, 114 SAEs were reported in the study.

The most common SAEs by SOC included "infections and infestations", "cardiac disorders", "gastrointestinal disorders" but in each group the percentages of subjects were below 1%.

No SAEs were assessed as related to the study vaccines.

Adverse Events leading to New Onset of Chronic Disease

The percentages of subjects who reported a new onset of Chronic Disease (NOCDs) were similar across the study groups (2.6% of subjects in the aQIV group, 3.6% in aTIV-1 group and 3.2% in aTIV-2 group). None of these events were considered related to the study vaccine

The most common SOCs for these were "Cardiac disorders" (0.5% to 0.9% subjects across study groups), "Musculoskeletal and connective tissue disorders" (0.3% to 1.1%) and "renal and urinary disorders" (0.2% to 0.7%). No imbalance between study groups was observed and the percentages of subjects were below 1% in each group.

Adverse Events of Special Interest (AESI)

In study V118_20, a total of 2 (0.1%) subjects had a reported AESI in the study; both AESIs occurred during the follow-up study period (Day 23 through Day 181). One subject in the aTIV-1 group developed Addison's disease and one subject in the aQIV group had polymyalgia rheumatica, both cases, the investigators conclude that these two AESIs were not related to the study vaccines.

Study V118_18

Deaths

Sixty seven deaths (33 in the aQIV group and 34 in the Boostrix group) occurred during the study and were considered by the investigator to be unrelated to the study vaccines.

Other Serious Adverse Events Two hundred thirty eight (7.0%) subjects in the aQIV group and 234 (6.9%) subjects in the Boostrix group reported at least one SAE during the study period; the proportions of subject with SAEs were similar between the vaccine groups.

One subject in the aQIV group experienced one SAE of rheumatoid arthritis. The event was considered moderate in intensity and possibly related to aQIV. One subject in the Boostrix group experienced two SAE, acute myocardial infarction, and ILI. Acute myocardial infarction was assessed as severe and possibly related to the vaccine. ILI was assessed as mild and probably related to the vaccine.

Adverse Events leading to New Onset of Chronic Disease (NOCDs)

The frequencies of unsolicited AEs leading to NOCDs were similar in the vaccine groups (9.5% in the aQIV and 9.0% in Boostrix group). AEs were heterogeneous in nature and consistent with clinical conditions spontaneously occurring in the elderly population.

Three AEs, reported for subjects in the aQIV group, were assessed to be possibly related to the study vaccines; (non-serious hyperglycaemia and radiculopathy and moderate rheumatoid arthritis).

Adverse Events of Special Interest (AESI)

Four subjects in the aQIV group and 6 subjects in the Boostrix group experienced AESIs. All AESIs, except one event of rheumatoid arthritis experienced by one subject in the aQIV group, were considered not related to study treatment.

Study V70_27

Deaths

A total of 98 subjects (1.4%) experienced SAEs with outcomes of death (52 subjects (1.5%) in the aTIV and 46 subjects (1.3%) in TIV). One subject (female, 70 years of age) who received the non adjuvanted TIV vaccine had an AE of Guillain-Barré syndrome (which developed 227 days after vaccination) that eventually led to death and was assessed by the investigator as possibly related to the study vaccine.

Other Serious Adverse Events

The percentage of subjects reporting SAEs were comparable overall, with a rate of 7% in each vaccine group through 1 year following vaccination

The most common SAEs by SOC included "infections and infestations" (2% each group), "cardiac disorders" (2% each group), the rest of SOC were reported with a percentage of subjects ≤1% in each group.

Adverse Events leading to New Onset of Chronic Disease

The percentages of subjects who reported a new onset of Chronic Disease (NOCDs) were the same in the study groups (6% each). None of these events were considered related to the study vaccine.

The most common SOCs for these were "vascular disorders", "metabolism and nutrition disorders", "musculoskeletal, connective tissue, and bone disorder" and "cardiac disorders" (1% in both groups for each of these categories).

Laboratory findings

Clinical Laboratory Evaluation

Pivotal study V118_20 and V118_18 did not include scheduled clinical laboratory assessments. No laboratory assessments of haematology, blood chemistry, or urine chemistry were specified in the protocol.

Pivotal study V70_27 included clinical laboratory assessments as a scheduled safety component. A further subset of 200 subjects (n=97 aTIV, n=103 TIV) was selected for safety laboratory testing on Day 1 (pre vaccination) and Day 8. Haematology tests included haemoglobin, platelet, red blood cell (RBC), and white blood cell (WBC) counts. Serum chemistry tests included alanine aminotransferase (ALT) and aspartate aminotransferase (AST). No clinically meaningful differences in group mean changes from baseline were observed between or within vaccine groups for laboratory parameters.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Overall, there were no clinically significant vital signs, physical findings, or other observations related to safety other than those reported as AEs or medical history

Safety in special populations

Intrinsic factor

Assessment of safety by subgroup is presented for study V118_20, V118_18 and V70_27. Subgroup analyses were performed for age, gender and race.

Age

In study V118_20, the percentage of subjects with solicited AEs was higher in the age group 65 to 74 years compared to those aged between 75-84 years: 47.5% versus 35.8% in the aQIV group and 27.7% versus 21.1% in the aTIV groups. In the age group ≥85 years rates with solicited were 38.7% and 32.3%. In study V118_18, the percentage of subjects with solicited AEs was higher in the age group 65 to 74 years compared to those aged between 75-84 years: 37.9% versus 14.5% in the aQIV group. In the aTIV study V70_27, subjects >75 years of age reported fewer reactions than subjects 65 to 75 years of age

Sex

In study V118_20, females reported more AEs (61.6 % versus 52.5%). Solicited AEs were also reported more frequently by females compared to males: 48.4% versus 37.7% in the aQIV group and 29.6% versus 21.0% in the aTIV group. In study V118_18 solicited AEs were slightly higher in females: 34.3% versus 31.0%. Solicited local and systemic adverse events were not presented by sex for study V70_27. Unsolicited adverse events were reported by relatively more females (n=765, 17%) than males (n=356, 14%).

Extrinsic factors

No subgroup analyses for extrinsic factors have been performed in study V118_20.

Evaluation of safety was performed **by country** for solicited and unsolicited AEs in study V118_18 and for unsolicited AEs in study V70_27. Overall, no notable findings were observed across vaccine groups.

Pregnancy and Lactation

Since aQIV is proposed for indication in individuals ≥65 years of age, use in pregnancy and lactation is not applicable. aQIV has not been studied in pregnant or lactating women. Similarly, aTIV has not been studied in pregnant or lactating women.

Immunological events

No cases have been identified. Overall, no safety concerns associated with vaccine-related hypersensitivity have been raised.

Safety related to drug-drug interactions and other interactions

Pivotal aQIV study V118_20 and V118_18 were not designed to prospectively assess interactions with concomitant vaccinations or drugs. However, there are data regarding the concomitant administration of Fluad (aTIV registered vaccine) with an approved 23-valent pneumococcal polysaccharide vaccine (PPSV23) and an approved 13-valent pneumococcal conjugate vaccine (PCV13) in older adults.

Discontinuation due to adverse events

In the study V118_20, no AEs leading to withdrawal were reported in the study

In study V118_18, the proportion of subjects who experienced any unsolicited AE that led to premature withdrawal was similar between the vaccine groups (1.1%). One AE, pyrexia, reported in the aQIV group at Day 24 was considered assessed as possibly related to vaccination.

In study V70_27, in each vaccine group, approximately 1% of subjects withdrew from the study prematurely due to 1 or more AEs (52 subjects in the aTIV group and 49 subjects in the TIV group; CSR V70_27, Table 14.3.2.4). Most of these withdrawals occurred because of death (52 subjects in aTIV died and 46 subjects in TIV died). There were no notable differences between the vaccine groups in percentages of subjects who withdrew

Analysis of Adverse Events upon Annual Revaccination: aTIV Revaccination Pooling

In the aTIV revaccination pooling studies, the assessment of the safety profile included 12 studies (5 primary and 7 revaccination studies). Subjects who received Vaccination 1 but did not receive a

subsequent vaccination in an extension study were also included in the pooling. The first (Vaccination 2) and second (Vaccination 3) revaccination dataset in the pooling only included data from a subgroup of subjects vaccinated in the primary vaccination study (Vaccination 1) who subsequently were enrolled in the revaccination studies.

Vaccination 1

Overall, solicited AEs after Vaccination 1 were higher in the aTIV group (41.5%) compared with the TIV group (34.8%). This difference was primarily due to the higher percentage of subjects reporting solicited local AEs in the aTIV group (22.9% aTIV versus 12.6% TIV).

Solicited systemic AEs were similar between the vaccine groups (15.1% aTIV versus 14.8%TIV). Unsolicited AEs were similar between the vaccine groups (17.8% aTIV and 21.0% TIV) as well as SAEs and AEs leading to hospitalization and SAEs leading to death.

Vaccination 2

The percentage of subjects reporting AEs after Vaccination 2 in all AE categories was higher after Vaccination 2 compared to Vaccination 1. The percentage of subjects reporting solicited AEs were comparable in the aTIV and TIV groups (48.8% aTIV and 45.8% TIV).

The percentage of subjects reporting unsolicited events after Vaccination 2 was 32.3% in the aTIV group and 41.2% in the TIV group, which was higher than after Vaccination 1 (15.7% aTIV and 15.8% TIV).

The percentage of subjects with SAEs following Vaccination 2 was comparable between the aTIV and TIV groups (6.1% aTIV and 5.5% TIV).

SAEs leading to death were generally low and were reported in 17 (3.5%) versus 6 (1.8%) subjects in the aTIV and TIV groups respectively.

Vaccination 3

The Vaccination 3 dataset (V7P3X2, V7P5X2) included data reported for the subset of subjects vaccinated in the first year (Vaccination 1) who subsequently received a second (Vaccination 2) and a third (Vaccination 3) vaccination of aTIV or TIV (aTIV N=150, TIV N=87).

After Vaccination 3, the percentage of subjects reporting AEs in all categories was lower than the AEs observed following Vaccination 1 and Vaccination 2.

SAEs were reported infrequently after Vaccination 3 and the percentages were similar between vaccine groups. There were no AEs leading to withdrawal or death reported following Vaccination 3.

Post marketing experience

Currently there are no post marketing data available for aQIV. Nevertheless, the post marketing safety experience after using aTIV compiles from 1st May 1997 to 31th May 2019 as recorded in the aTIV Periodic Safety Update Report (PSUR). During this period, over 127 million doses of aTIV were distributed, and 4,376 spontaneous/literature aTIV-confirmed individual case safety reports (ICSR) were received.

The three most commonly reported SOCs (≥10%) overall were general disorders and administration site conditions (33.55%), injury, poisoning and procedural complications (13.72%) and musculoskeletal and connective tissue disorders (10.96%). Analysis of important identified and potential risks for aTIV as compared to TIV using disproportionality method (PRR) shows no risks fulfilling criteria for a serious drug reaction (Table 67). A sensitivity analysis restricting cases containing older adults shows no change in risks fulfilling criteria for an SDR.

Table 66: Proportional Reporting Rate and Two-sided 95% CI of Important Identified and Potential Risks for aTIV Compared with Agrippal; Older Age Group (⩾65 years) (Cumulative to 31 May 2019)

Risk	n ICSR aTIV N = 3238	n ICSR Agrippal N = 492	PRR	95% CI
Anaphylaxis	21	3	1.06	0.32 to 3.55
Bell's palsy	9	3	0.46	0.12 to 1.68
Convulsion	12	7	0.26	0.10 to 0.66
Demyelination	48	22	0.33	0.20 to 0.54
Encephalitis	10	10	0.15	0.06 to 0.36
Guillain-Barre syndrome	49	19	0.39	0.34 to 0.95
Haemolytic anaemia	7	1	1.06	0.13 to 8.63
Immune thrombocytopenic purpura	13	9	0.22	0.09 to 0.51
Neuritis	3	2	0.23	0.04 to 1.36
Vaccination failure	58	15	0.59	0.34 to 1.03
Vasculitis	24	6	0.61	0.25 to 1.48

Abbreviations: aTIV = adjuvanted Trivalent Influenza Vaccine; CI = confidence interval; ICSR = individual case safety reports; N= number of ICSR; PRR = Proportional Reporting Rate.

2.7.1. Discussion on clinical safety (elderly indication)

The safety profile of aQIV in elderly has been evaluated in 4,269 subjects ⩾ 65 years of age. Furthermore, it is supported by study data from aTIV in more than 5,000 subjects as well as over 20 years of postmarketing data with aTIV.

Overall, the clinical development program to support registration of aQIV in individuals 65 years of age and above builds on a pivotal aQIV study (V118_20), the phase III study V118_18, the pivotal aTIV study (V70_27), several supportive aTIV revaccination studies (12 supportive studies) and the cumulative post marketing experience with aTIV.

The total size of the aQIV safety database in the group of >65 years of age is in line with the "Guideline for the evaluation of new vaccines" (EMEA/CHMP/VWP/164653/2005) recommendation. Additionally, the safety data provided in all supportive studies accounted of 5,146 adult subjects receiving the aTIV licensed vaccine (Fluad) or aTIV-2 (containing the alternate B strain) support the safety data set of subjects receiving the aQIV.

Demographic and baseline characteristics

The demographic and baseline characteristics were generally comparable between vaccine groups in V118_20, V118_18 and V70_27. However, in V118_20 the median BMI (body mass index) was high in all study groups, ranging from 28.62 to 28.96, comparing V70_27 (ranging from 25.32 to 25.40).

The data of the percentage of subjects having at least one disorder recorded in their medical history in both studies have been provided. These data are slightly lower in V70_27 (86.6%) than in V118_20 (97.7%) and in V118_18 (90.6%).

The percentages of subjects having one or more concomitant medication in the pivotal V118_20, phase III V118_18 and V70_27 are similar across vaccine groups. Lower percentages have been observed in

subjects included in the V70_27. The different populations enrolled in each study could explain this difference.

Solicited Adverse events

In the pivotal Study V118_20, similar rates of solicited events from Day 1 to Day 7 after vaccination were observed in adults who received aQIV or aTIV (51.8% in aQIV group, 48.2% to 48.7% in aTIV comparator groups).

The most common reported solicited AE for aQIV was injection site pain, reported by 31.9%, followed by fatigue (16.0%) and headache (12.0%). Most solicited reactions were reported as mild or moderate in intensity and resolved within the first 3 days after vaccination.

When the safety profile of aQIV is compared to that of aTIV, the percentage of subjects with solicited adverse events was slightly higher in the aQIV group compared to the aTIV groups. This is mainly driven by the local solicited adverse events. No remarkable differences in frequencies of moderate and severe solicited local and systemic AEs were observed across aQIV and aTIV groups. The use of analgesics and/or antipyretics for prevention or treatments of pain and/or fever were low but higher in aQIV group than in one comparator vaccine (5.4%, 2.7%, 3.9% in the aQIV, aTIV-1, and aTIV-2 groups, respectively).

These findings indicate that the addition of the fourth influenza strain causes a numerical increase in mainly local reactogenicity of aQIV compared to aTIV. However, this difference is small and concerns mostly AEs of mild intensity and short duration and is therefore considered acceptable.

The reactogenicity of the vaccine within 30 minutes postvaccination was insignificant, with no difference between vaccine groups overall, by age groups and by gender.

In the pivotal Study V70_27**,** the reactogenicity profile was higher in subjects who received aTIV vaccine than TIV (46% in aTIV group and 33% in the TIV group). The higher percentage in solicited AEs for the aTIV group was primarily due to a higher incidence of pain and tenderness at the injection site, as well as myalgia following vaccination with aTIV, indicating that the addition of the adjuvant causes a clear increase in reactogenicity of the aTIV compared to TIV. In the pivotal study V70_27 no difference in the use of analgesics or antipyretics for prevention or treatment between aTIV and comparator TIV were observed.

In study V118_18, similar rates of subjects reporting any solicited AE from Day 1 through Day 7 after vaccination were observed: 34.3% in the aQIV group and 32.2% in the Boostrix group. The proportions of subjects with local and systemic AEs were slightly higher in the aQIV group compared to the Boostrix group (24.4% vs. 19.6% for local reactions, and 19.2% vs. 16.3% for systemic reactions, respectively). The majority of local AEs were of mild or moderate intensity.

The most common reported local solicited AE for aQIV was injection site pain, reported by 16.3%, followed by erythema (10.8%) and induration (10.3%). Most solicited reactions were reported as mild or moderate in intensity and resolved within the first 3 days after vaccination.

The most commonly reported systemic solicited AEs were headache (10.8%), fatigue (10.5%), and myalgia (7.7%).

When comparing the data between this study and pivotal study V118_20, overall a lower percentage of subjects experiencing solicited AEs has been observed in this additional study V118_18 (34.3% and 51.8% in V118_18 and V118_20 respectively for any solicited AEs). Not only it has been observed for any solicited AE but also for every AE reported separately (each solicited listed AE, local and systemic). Moreover, these new data have been reported as lower than the ones observed in the other pivotal study V70_27, where subjects were exposed to the aTIV vaccine. As a response to the D180 LoOI it is not

obvious that a change in the antigens could be responsible of the different reactogenicity observed in different trials. It can be assumed that some differences in number of reported adverse reactions can be due to the clinical trial being conducted in different countries and in different populations.

Unsolicited Adverse Events

The percentage of unsolicited AEs reported in V118_20 and V118_18 were very similar across the vaccine groups and between the data reported in the pivotal study V70_27.

In pivotal study V118_20, at least 1 unsolicited AE was reported during the entire study period by 19.8% of subjects in the aQIV group. The most commonly reported unsolicited AEs were influenza-like illness (2.0%), injection site bruising (1.1%), injection site erythema (0.7), upper respiratory tract infection (0.7%), and headache (0.6%). There were 39 subjects (4.4%) with an unsolicited AE considered possibly related to treatment, which mostly included injection site bruising (1.0%), and injection site erythema (0.7%).

No cases of immediate hypersensitivity reactions 30 minutes after vaccination have been identified in studies V118_20, V118_18 and V70_27.

In V118_18, the proportion of subjects with unsolicited AEs that were assessed as related to the study vaccine were similar, although slightly higher in aQIV vs the Boostrix group (9.0% vs 7.7%, respectively). ILI was the most frequently reported unsolicited AE by Preferred Term (PT) in the aQIV and Boostrix groups (4.6%).

Serious adverse events and deaths

There were no deaths judged related to aQIV. Two deaths in the study V118_20 and 33 deaths in the study V118_18 occurred in the aQIV group, none of these deaths was considered related to the vaccine. Based upon the information in the narratives for both subjects, this assessment can be agreed.

A total of 98 deaths were reported during the V70_27; one case of Guillain-Barré syndrome was considered possibly related to the non adjuvanted vaccine (TIV).

In V118_20 there were no SAEs judged related to aQIV.

In study V70_27 there was one SAE judged by the investigator as possibly related to aTIV, namely as a case of bronchitis with onset 8 days after receipt study vaccine. There was no medical history of bronchitis. As there is no pathophysiological mechanism to explain this AE, it is considered unlikely that bronchitis is possibly related to the vaccine.

In V118_18one subject in the aQIV group experienced one SAE of rheumatoid arthritis. The event was possibly related to aQIV.

The frequencies of unsolicited AEs leading to NOCDs were similar in the vaccine groups in study V118_18. Three AEs, reported for subjects in the aQIV group, were assessed to be possibly related to the study vaccines (non-serious hyperglycaemia and radiculopathy and moderate rheumatoid arthritis).

The percentage of subjects with medically attended AEs within 30 days after the first occurrence of RT-PCR confirmed influenza-like illness (ILI) showed rates generally similar in the aQIV group (0.7% subjects) and Boostrix group (0.4% subjects).

Adverse events of special interest

The occurrence of new onset of chronic disease was well balanced between study groups in the studies V118_20, V118_18 and V70_27. None of these events were considered related to the study vaccine (aQIV or aTIV) in V118_20 and V70_27.

In V118_18, four subjects in the aQIV group and 6 subjects in the Boostrix group experienced AESIs. All AESIs, except one event of rheumatoid arthritis experienced by one subject in the aQIV group, were considered not related to study treatment.

Special subgroups

Age

It is expected that with increasing age the reactogenicity decreases. This was indeed observed in study V118_18 and V70_27 but not in study V118_20. However, it should be noted that the number of subjects included ≥ 85 years of age in study V118_20 was very small, therefore no firm conclusions can be drawn.

Gender

In study V118_20 overall female reported more AEs compared to male (for aQIV any 61.6 % versus 52.5% for female and male, respectively). Also, solicited local and systemic AEs were more frequently reported by female for aQIV 48.4% and 29.6% versus 37.7% and 21.0% for male. Indicating that the vaccine is somewhat more reactogenic in female compared to male.

For study V70_27 and V118_18 reactogenicity was slightly higher in females as compared to males, both for solicited local as solicited systemic reactions. A similar pattern is seen for the unadjuvanted influenza vaccine included in study V70_27

Safety in special populations

Safety in special populations (immunocompromised individuals, pregnant, breast feeding women) has not been analysed.

Since aQIV is proposed for indication in individuals ⩾65 years of age, the use in pregnancy and lactation is not applicable.

Immunocompromised individuals have been considered as an exclusion criterion in the aQIV study and have been included as missing information.

Revaccination

There are no revaccination data with aQIV in the population of older adults.

Data obtained with aTIV suggests that reactogenicity of aTIV and TIV increases after the second vaccination. The percentage of subjects with solicited AEs is still within a range that can be expected after vaccination (48.8% and 45.8%), and the increase from the first to the second season is similar for aTIV and TIV. Following the third vaccination the rate decreased. However, it should be noted that the numbers after the third vaccination are rather low so no firm conclusions can be drawn. This data does not preclude the use of aQIV for revaccination in the elderly.

Post marketing data

Post marketing data with aTIV showed that the observed AEs post marketing were in line with the safety profile described in the studies. Most AEs are general disorders and administration site conditions.

When the Proportional Reporting Rate of important identified and potential risks for aTIV was compared with TIV no risks fulfilling the criteria for a signal of disproportionality reporting was observed. Indicating that the addition of the adjuvant did not influence the important identified and potential risks.

In summary, the aQIV studies demonstrated that the addition of a fourth strain does not alter the safety profile of aQIV. The safety profile of aQIV was slightly worse versus aTIV with no statistical significance, so they are considered to be similar. Minimal differences were observed in rates of solicited events and unsolicited AEs judged by the investigator as possibly/probably related between aQIV and aTIV. No new

safety signals were detected. The reactogenicity of the vaccine within 30 minutes postvaccination was insignificant, with no difference between vaccine groups overall, by age groups and by gender, and overall, no safety concerns associated with vaccine-related hypersensitivity have been raised.

No SAEs, NOCD and deaths in adult population were judged by the investigator as possibly/ probably related to the study vaccine. Except in V118_18, where one subject in the aQIV group experienced one SAE of rheumatoid arthritis, possibly related to aQIV. One subject in the Boostrix group experienced two SAE, acute myocardial infarction and ILI, assessed as possible and probably related to the vaccine respectively.

Safety in special populations and drug interactions have not been analysed in aQIV studies.

2.7.2. Conclusions on the clinical safety (elderly indication)

After the review of the submitted data collected in the pivotal aQIV study (V118_20), the pivotal aTIV study (V70_27), the study V118_18, and the supportive aTIV revaccination studies it can be expected that the aQIV safety profile would be in general comparable to that of the aTIV comparators. No new safety signal has been observed in the submitted clinical database. It can be concluded that the increase in antigen amount due to the additional B strain does not have any clinically relevant impact in the safety of the vaccine.

The safety profile of aQIV is considered adequate to support the indication for the prophylaxis of influenza in subjects≥65 years of age.

2.8. Risk Management Plan

Safety concerns

No safety concerns have been identified in the RMP of Fluad Tetra. This is considered appropriate.

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
A non-interventional study of vaccine effectiveness; aQIV versus no vaccination in elderly ⩾ 65 years (DRIVE sub-analysis).	To perform an analysis of influenza vaccine effectiveness of aQIV vaccination versus no vaccination in elderly ⩾ 65 years	Measure of vaccine effectiveness in routine care.	Planned for the initial influenza season of launch.	First annual submission of results planned in December following the initial season of launch and annually thereafter

The effectiveness study will provide annual brand-specific estimates, in line with the EMA guidance.

Risk minimisation measures

No risk minimisation activities are considered warranted, as there are no safety concerns identified in the RMP of Fluad Tetra.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.9. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

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

The PSUR should be submitted in compliance with the currently existing EURD list entry for "'influenza vaccine (surface antigen, inactivated, adjuvanted)".

2.10. New Active Substance

The applicant declared that influenza vaccine (surface antigen, inactivated, adjuvanted) has not been previously authorised in a medicinal product in the European Union.

Fluad Tetra is a seasonal adjuvated quadrivalent influenza vaccine (aQIV). aQIV is a surface antigen inactivated influenza vaccine containing influenza surface antigens (haemagglutinin (HA) and neuraminidase (NA)) from each of the four influenza strains (Type A/H1N1, Type A/H3N2 and Type B Yamagata Lineage and Victoria Lineage), recommended annually by the WHO and subsequently CHMP for the EU market. The adjuvant is MF59C.1. (MF59), a squalene-based oil-in-water emulsion previously approved for human use in Fluad (trivalent seasonal, adjuvated inactivated influenza vaccine, aTIV).

According to the applicant, the active substance in Agrippal and Fluad is a combination of HA and NA surface antigens from each of the three influenza strains recommended annually by the WHO for trivalent influenza vaccines.

Also the applicant stated that the active substances in aTIV and aQIV differ by the presence of HA and NA of a second B strain in aQIV and aQIV has not yet been approved. The active substance in aQIV (combination of HA and NA surface antigens from each of the four influenza strains recommended annually by the WHO for quadrivalent influenza vaccines) was therefore claimed as a new active substance, aQIV. The combination of this new active substance with adjuvant MF59, was claimed to be a new drug product.

However, based on the initial review of the data by CHMP, the active substances contained in the medicinal product Fluad Tetra were not qualified as a new active substance in comparison to the products previously authorised in the European Union (Fluad and Agrippal) for the following reasons:

- The product contains four active substances, not one active substance from a combination of four different strains, as claimed by the applicant. It has to be noted that strains from both lineages of influenza B have been components of approved trivalent influenza vaccines in previous influenza seasons, i.e. no new lineage of influenza B which could be qualified as

NAS, is included in the Fluad Tetra composition. The same applies to the two influenza A subtypes.

- The active substance manufacturing process is similar to the one registered for Fluad and Agrippal. This does not result in a novel type of active substance.
- Influenza vaccines have a specific legal provision which permits change of the influenza antigens without leading to a new MA every influenza season even if a new influenza strain is included in an authorised vaccine. Therefore, qualification of the active substance of Fluad Tetra as NAS would thus be inconsistent with the legal provision.
- From a regulatory perspective, an adjuvant is not part of the active substance(s). Therefore the adjuvant MF59C.1 (MF59) in Fluad Tetra cannot be considered in the context of the NAS assessment.
- The active substances in Fluad Tetra do not differ significantly in properties with regard to safety and efficacy from the previously authorised substances.

The CHMP's scientific objection to this claim was classified as a major objection. The NAS application was withdrawn by the Applicant. Thus, this application does not now include a new active substance claim.

2.11. Significance of paediatric studies

Not applicable.

2.12. Product information

2.12.1. User consultation

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

2.12.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Influenza is an infectious acute respiratory disease of global importance that occurs in annual epidemics in the northern hemisphere (NH) and southern hemisphere (SH). The influenza virus is transmitted by respiratory droplets or aerosols containing the influenza virus particles and subsequent inhalation of infectious particles or self-inoculation from a contaminated surface. Clinical manifestation of influenza virus infection is characterized by an abrupt onset of nonspecific respiratory and systemic effects, such as fever, myalgia, headache, malaise, non-productive cough, sore throat and rhinitis.

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, in part due to the age related decline of the immune response (immunosenescence)), 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.

3.1.2. Available therapies

Vaccination is considered the best approach to lower the burden of influenza disease. Different seasonal inactivated (split virion or subunit) influenza vaccines (quadrivalent and trivalent) are licensed for children aged 6 months and older, adolescents and adults, as well as a Live Attenuated Influenza Vaccine licensed for children and adolescents aged 2 years to 17 years.

Differences between the circulating strains and those included in the vaccine as a result of antigenic drift poses another key challenge for conventional influenza vaccines as it decreases vaccine efficacy. This is particularly relevant since A/H3N2 shows a high rate of evolution among the influenza subtypes currently circulating with antigenically distinct strains emerging on average every 2 to 5 years.

In elderly, immune responses against conventional (trivalent) inactivated influenza vaccines has been shown to be lower than in younger adults due to immunosenescence. In line with this, clinical vaccine efficacy estimates were lower in older adults (17% to 53 %) as compared to younger adults (70% to 90%) (Goodwin et al. 2006). Therefore, there is a need for improved influenza vaccines for these age groups, i.e. children and elderly.

3.1.3. Main clinical studies

The clinical development program to support licensure of aQIV in individuals ≥65 years of age is based on the results of the pivotal aQIV immunogenicity and safety study V118_20. The data package also includes a key supportive aTIV study V70_27.

In addition, 7 supportive aTIV studies, 7 aTIV revaccination studies, and 2 aTIV effectiveness studies were submitted. Additionally, the safety profile is supported by more than 20 years of aTIV postmarketing data.

Moreover, data from study V118_18 was submitted during the evaluation.

V118_20 is a randomised controlled double blind multicentre study in 1,778 adults ≥65 years which set out to demonstrate non-inferiority of the immune responses to the aQIV vaccine as compared to adjuvanted trivalent influenza vaccines (Fluad, aTIV 1, and an aTIV containing the alternate B strain, aTIV-2), forming the bridge to the evidence generated with aTIV.

V70_27 is a randomised controlled observer-blind multicentre study in 7,109 adults ≥65 years of age, which set out to demonstrate superiority of the immune response to the MF59 adjuvanted trivalent influenza vaccine Fluad (aTIV, subject to receive either 1 of the 3 lots of aTIV (lots 1, 2, or 3)) as compared to a non-adjuvanted trivalent inactivated vaccine (TIV).

3.2. Favourable effects

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

Data derived from aTIV are considered directly relevant to aQIV because although aQIV contains additional antigen, the same active substance is used in both vaccines, both vaccines contain the same amount of MF59, and the manufacturing process.

In study V118_20, non-inferiority of aQIV over aTIV could be claimed as the estimated GMT ratio (aTIV/aQIV) against homologous strains contained in aTIV was 1.16 (95% CI 1.05, 1.27) for A/H1N1, 0.99 (95% CI: 0.90, 1.09) for H3N2, 0.99 (95% CI 0.90, 1.08) for B/Yamagata and 0.99 (95% 0.90, 1.08) for B/Victoria. The estimated difference in SCR (aTIV-aQIV) was 3.23 (95% CI -1.30, 7.76), 0.37 (95% CI: -4.23, 4.96), -0.93 (95% CI -5.13, 3.27) and -1.26 (95% CI -5.07, 2.55) for the four strains respectively.

In terms of immunogenicity, the primary endpoint was met, and showed that aQIV elicited a non-inferior immune response as compared to aTIV-1 and aTIV-2 in terms of GMT ratios and differences in SC rates. Additionally, the secondary endpoint regarding immunologic superiority of aQIV relative to aTIV for the alternate B strain was also met.

In study V70_27, the estimated GMT ratio (aTIV/TIV) against homologous strains 21 days after vaccination was 1.37 (95% CI: 1.29, 1.46) for A/H1N1, 1.6 (95% CI: 1.51, 1.68) for A/H3N2, and 1.14 (95% CI: 1.08, 1.2) for the B strain. The estimated difference in seroconversion rate (SCR, aTIV-TIV) was 9.6% (95% CI: 7.4, 11.8), 13.8% (95% CI: 11.7, 16) and 3% (95% CI: 1%, 5%) for the three strains respectively. Non-inferiority was demonstrated for GMT ratios and SCR differences for all 3 strains.

For heterologous strains, the estimated difference in SCR was 12.8% (95% CI: 8.4, 17.2) for A/H1N1, 12.5% (95%CI: 0.1, 17) for A/H3N2, and 4.2% (95%CI: 0, 8.4) for the B strain. GMT ratios were 1.49 (95% CI: 1.29, 1.72), 1.38 (95% CI: 1.24, 1.52) and 1.09 (95%CI: 0.99, 1.21) for the three strains respectively.

After 181 days after vaccination, the estimated GMT for the response against homologous A/H3N2 and B were higher in the aTIV group compared to the TIV group. This was also seen for the A/H3N2 strain 366 days after vaccination (GMT ratio 1.3 (95% CI 1.01, 1,67), but not for the B strain. There was no important difference for A/H1N1 between both groups at both time points; the estimated GMTr was 1.05 (95% CI: 0.82, 1.33) and 0.94 (95%CI: 0.73, 1.22) at D181 and D366 respectively.

In a posthoc analysis, it was shown that aTIV elicited significantly higher GMT levels and SCR than TIV against all 3 homologous strains, demonstrating the benefit of the MF-59 adjuvant in subjects ≥65 years of age.

3.3. Uncertainties and limitations about favourable effects

Although the HI response was higher in subjects who received aTIV as compared to those who received TIV in study V70_27, superiority could not be claimed according to the predefined superiority criteria. The clinical relevance of the superiority in terms of increased HI titres following vaccination with the adjuvanted inactivated influenza vaccine as compared to non-adjuvanted inactivated influenza vaccine is not known, but it is expected that higher HI titres will translate into a better protection against the strains included in the vaccine.

There are no data in elderly with a compromised immune system, and little data in the frail elderly.

The applicant has presented the CSR for study V118_18, aimed at evaluating the efficacy, safety and immunogenicity of aQIV compared to an non-influenza comparator in adults ≥ 65 years of age. In this study, the primary objective of demonstrating the efficacy of aQIV in adults 65 years and above in protecting against any RT-PCR confirmed influenza A and/or B diseases was not met, since the pre-specified statistical success criterion (the LL of the two-sided 97.45% CI of VE should exceed 40%) was not satisfied. Similarly, the key secondary objective was not met. Therefore, this study could not support to the demonstration of efficacy in the ≥65 age group.

Two other limitations that affect all influenza vaccines are:

- The efficacy depends on the degree of antigenic match between vaccine and circulating strains and therefore the efficacy of the seasonal influenza vaccines could vary in different seasons.
- In general, all influenza vaccines, show reduced efficacy (in terms of immunogenicity) in the elderly due to immune senescence. However, the immunogenicity results obtained with Fluad Tetra in subjects >65 years of age were similar with results obtained with the authorised aTIV, indicating similar acceptable levels of efficacy.

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

3.4. Unfavourable effects

The safety of Fluad Tetra in elderly subjects 65 years of age and older was evaluated in two clinical studies (V118_20 and V118_18), in which 4,269 received Fluad Tetra.

Following vaccination with aQIV, in study V118_20, 51.8% of subjects ≥65 years reported at least one solicited AE, of whom 43.6% a local solicited AE and 26.2% a systemic solicited AE. The most common solicited AEs were injection site pain (31.9%), fatigue (16.0%) and headache (12.0%).

In study V118_18, lower percentage of subjects experiencing solicited AEs than in the pivotal study V118_20 (34.3%, of whom 24.4% a local solicited AE and 19.2% a systemic solicited AE). The most common reported solicited AE for aQIV was injection site pain (16.3%), erythema (10.8%), headache (10.8%), and induration (10.3%).

It can be expected that the aQIV safety profile would be in general comparable to that of the aTIV comparators. No new safety signal has been observed in the submitted clinical database. It can be concluded that the increase in antigen amount due to the additional B strain does not have any clinically relevant impact in the safety of the vaccine.

3.5. Uncertainties and limitations about unfavourable effects

There is a safety database with aQIV, which is limited in size to determine the occurrence of rare (<0.1%) adverse events. In the studies in elderly, subjects were generally healthy with few comorbidities and it is likely that the extremely frail elderly were excluded.

3.6. Benefit-risk assessment and discussion

The immunogenicity of Fluad (trivalent formulation) is relevant to Fluad Tetra because both vaccines are manufactured using the same process and have overlapping compositions.

It has been demonstrated that aTIV has an immunological benefit over non-adjuvanted influenza vaccine in adults ≥65 years, as three weeks after vaccination an increased HI response to all three homologous strains was observed. The size of this benefit was variable between strains and sustained over 12 months for one of the three strains. As non-inferiority between aQIV and aTIV with two alternating B strains has been demonstrated, the findings with aTIV can be extrapolated to aQIV. Whether this immunogenic benefit translates into better protection is not known. Studies with aTIV submitted as supportive have pointed towards a clinical benefit of the adjuvanted inactivated influenza vaccine over non-adjuvanted inactivated influenza vaccines, in terms of decreased hospitalisation. According to the CHMP guideline for influenza vaccines (Non clinical & clinical module) it is sufficient for this population to demonstrate an advantage in terms of immune responses to justify the inclusion of an adjuvant. The increase in reactogenicity due to the inclusion of the adjuvant is within limits and reactions remain mostly mild to moderate and transient.

As an immunological advantage of the adjuvant has been demonstrated in comparison to a non-adjuvanted influenza vaccine and as the reactogenicity observed in clinical trials is, albeit increased compared to non-adjuvanted inactivated influenza vaccines, within limits of what can be expected for influenza vaccines, the Benefit Risk balance can be considered positive.

3.7. Conclusions

The overall B/R of Fluad Tetra is positive.

4. Recommendations

Outcome

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

"*Prophylaxis of influenza in the elderly (65 years of age and older).*

Fluad Tetra should be used in accordance with official recommendations."

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

Conditions or restrictions regarding supply and use

Medicinal product on medical prescription for renewable or non-renewable delivery.

Official batch release

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

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

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0057/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC).