17 October 2024
EMA/511487/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fluad

International non-proprietary name: influenza vaccine (surface antigen, inactivated, adjuvanted)

Procedure No. EMEA/H/C/006538/0000

Note

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

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List of abbreviations

AGRC	Strains undergoing the ultrafiltration concentration pathway
AE	Adverse event
AEFI	Adverse events following immunisation
AESI	Adverse events of special interest
aQIV	Adjuvanted quadrivalent influenza vaccine
AS	Active substance
aTIV	Adjuvanted trivalent influenza vaccine
AUC	Area under the curve
BPC	Bio process containers
CBER	Center for Biologics Evaluation and Research
CDC	Center of Disease Control and Prevention
CDP	Clinical Development Plan
CI	Confidence of interval
CMI	Cell mediated immunity
CoA	Certificates of analysis
COPD	Chronic obstructive pulmonary disease
CPP	Critical process parameters
CSR	Clinical study report
CT	Clinical trial
CTAB	Cetyltrimethyl-ammonium bromide
CTD	Common technical document
DMC	Data Monitoring Committee
ELISA	Enzyme-linked immunosorbent assay
ELLA	Enzyme-linked lectin assay
ER	Event rate
FAS	Full analysis set
FSFV	First subject, first visit
GLIMS	Global laboratory management system
GMP	Good manufacturing practice
GMT	Geometric mean titre
HA	Hemagglutinin
HI	Hemagglutination inhibition
HR	Hazard ratio
IIV	Inactivated influenza vaccines
ILI	Influenza-like illness
IRT	Interactive response technology
IPCs	In-process controls
LL	Lower limit
LSLV	Last subject, last visit
MAA	Marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
MFAS	Modified full analysis set
MF59	MF59C.1 adjuvant
MPH	Monovalent pooled harvest
MRP	Mutual recognition agreement
MS	Master seed
NA	Neuraminidase
NAS	New active substance

NH	Northern hemisphere
NOCD	New onset chronic diseases
NP	Nasopharyngeal
PACMP	Post-approval change management protocol
PBS	Phosphate-buffered saline
Ph. Eur.	European Pharmacopoeia
PPQ	Process performance qualification
PPS	Per protocol set
PT	Preferred term
QA	Quality attributes
QIV	Quadrivalent influenza vaccine
RH	Relative humidity
RT-PCR	Reverse transcription-polymerase chain reaction
rVE	Relative vaccine efficacy
SAE	Serious adverse event
SH	Southern hemisphere
SmPC	Summary of product characteristics
SOC	System organ class
SPF	Specified-pathogen-free embryonated eggs
SRID	Single radial immunodiffusion
TIV	Trivalent influenza vaccine
TSE	Transmissible spongiform encephalopathies
UF	Ultrafiltration
UL	Upper limit
VE	Vaccine efficacy
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 3 June 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Fluad, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 March 2024. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication *"Prophylaxis of influenza in adults 50 years of age and older. Fluad should be used in accordance with official recommendations"*.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0180/2024 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Sol Ruiz Co-Rapporteur: Patrick Vrijlandt

The application was received by the EMA on	3 June 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 September 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2024
The Rapporteurs circulated the Joint Assessment Report to all CHMP members on	10 October 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Fluad on	17 October 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Influenza is a highly contagious infectious disease that occurs in epidemics throughout the winter months in temperate climates in the Northern and Southern hemispheres. The influenza virus is an orthomyxovirus with two clinically relevant types (types A and B).

Influenza is characterised by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, non-productive cough, sore throat, and rhinitis (Temte and Prunuske 2010) and generally resolves within 2 to 7 days. However, influenza can exacerbate underlying medical conditions and/or lead to secondary viral or bacterial pneumonia for some people, notably older adults and those with chronic diseases (including pulmonary or circulatory disorders, metabolic disorders such as diabetes mellitus, renal dysfunction, or immunosuppression) (Rothberg et al. 2008; Fiore et al.2009).

2.1.2. Epidemiology, risk factors and prevention

All age groups can be affected but there are groups that are more at risk than others.

People at greater risk of severe disease or complications when infected are pregnant women, children under 5 years of age, older people, individuals with chronic medical conditions (such as chronic cardiac, pulmonary, renal, metabolic, neurodevelopmental, liver or haematologic diseases) and individuals with immunosuppressive conditions/treatments (such as HIV, receiving chemotherapy or steroids, or malignancy)

The burden of influenza disproportionately falls on individuals <5 years of age and ≥65 years of age (Neuzil et al. 2000; Thompson et al. 2004; Rolfes et al. 2016). 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 hospitalisations and deaths. In the United Kingdom (UK), influenza-related hospitalisation rate was estimated to be 101/100,000 for individuals 65 to 74 years of age, and 252/100,000 for individuals ≥75 years of age relative to the overall rate of 49/100,000 (Matias et al. 2016).

Similarly, in the United States (US), the influenza-related hospitalisation rate over 15 seasons was estimated to be 309/100,000 in individuals ≥65 years of age versus a mean of 63.5/100,000 across all age groups (Zhou et al. 2012). Influenza-related hospitalisation in older adults is associated with reduced mobility and quality of life, as well as functional decline, resulting in dependency on home caregivers or nursing homes (Hirsch et al. 1990; Creditor 1993; de Vos et al. 2012). Influenza also contributes substantially to the mortality rate among ≥65 years of age. In the US, between 3,300 to 48,600 deaths occur annually from influenza-related causes with approximately 90% of these deaths occurring in individuals ≥65 years of age (CDC 2010; Thompson 2003). 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 (Iuliano 2018).

Regarding the burden of influenza in the 50 to 64 years of age group in Europe, the impact of seasonal influenza on hospitalisations and mortality was evaluated for 10 influenza seasons between 1996 and 2006 in five European countries (Netherlands, United Kingdom, France, Portugal, and Spain), using a Poisson regression model with age-specific consultation rates for influenza-like illness and acute respiratory infection. For hospitalisations, the percentage of admissions due to respiratory disease caused by influenza activity for the 50- to 64-years age group ranged between 2.7% and 4.8% and the percentage of admissions due to pneumonia and influenza ranged between 3.3% and 12.3%. The percentage of mortality due to respiratory disease caused by influenza activity was similar for the age groups 50 to 64 years and 65 years and older, 9.4%-19.4% and 9.4%-19.3%, respectively, as was the percentage of mortality due to pneumonia and influenza caused by influenza activity 11.8%-24.5% and 12.1%-25.1%, respectively (NIVEL, 2010).

In the US, there are approximately 63 million people between 50 and 64 years of age, of which approximately one-third have an underlying medical condition that increases their risk for complications from influenza disease (CDC 2019). In the US, the estimated rate of hospitalisations due to influenza disease is 3-fold higher in adults 50 to 64 years of age compared to the younger adult (18-49 years) age group (121.3 vs 39.8 per 100,000 population).

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

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

2.1.3. Aetiology and pathogenesis

The influenza virus is an orthomyxovirus that can be classified into 3 biologically similar, but antigenically different types that are known to infect and cause disease in humans, A, B, and C, of which type A and B viruses are the most clinically significant. The influenza type A virus can be further divided into subtypes based on the hemagglutinin (HA) and neuraminidase (NA) surface glycoprotein antigens. The subtype refers to major antigenic variation with respect to the HA and/or NA virion antigens.

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

2.1.4. Clinical presentation, diagnosis

Clinical manifestation of influenza virus infection is characterised 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).

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

2.1.5. Management

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

Vaccination is considered the best strategy to lower the burden of influenza disease. However, the efficacy of influenza vaccines in older individuals is significantly lower than in younger individuals due to the aging of the immune system as well as underlying medical conditions, factors which increase the risk of influenza complications and interfere with immune responses.

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

Vaccines against seasonal influenza may need to be updated in composition on a yearly basis to include the latest circulating viruses and why people need to get vaccinated accordingly. The protection afforded by conventional influenza vaccines is driven by how well the strains in the vaccine match the viruses that circulate during influenza season (antigenic match).

2.2. About the product

Adjuvanted Trivalent Influenza Vaccine (aTIV; Fluad) is an egg-derived, surface antigen, inactivated influenza vaccine, adjuvanted with MF59C.1 , a squalene-based oil-in-water emulsion.

aTIV belongs to the pharmacotherapeutic group of viral vaccines (influenza vaccines). The Anatomical Therapeutic Chemical code is J07BB02 (Influenza, inactivated, split virus or surface antigen).

The active substance comprises virus surface antigens (haemagglutinin [HA] and neuraminidase [NA]) of the 3 strains of influenza virus recommended by the World Health Organization (WHO) for the corresponding influenza season:

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

aTIV contains a standard amount of 15 µg of HA of each viral strain per 0.5 mL dose. The formulation contains 9.8 mg of MF59C.1 per dose.

The claimed indication for aTIV is for prophylaxis of influenza in persons 50 years of age and older based on the evidence from the clinical development of aTIV and aQIV. The data generated during development of aQIV is relevant to aTIV because both vaccines are manufactured using the same process and have overlapping compositions.

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

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

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

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

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

2.3. Quality aspects

2.3.1. Introduction

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

Fluad (adjuvanted trivalent influenza vaccine, aTIV) is provided in a pre-filled syringe containing a single dose of 0.5 mL sterile suspension for injection (dose). Each dose of aTIV contains a nominal total of 45 µg of antigens per 0.5ml dose; 15 µg of HA from each of the influenza virus strains (of A/H1N1 subtype; A/H3N2 subtype and B/Victoria lineage) 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, sodium citrate – citric acid buffer and polysorbate and sorbitan trioleate.

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

The product is available in pre-filled syringes (type I glass) with a plunger stopper (bromobutyl rubber), presented with or without needle. Each pre-filled syringe contains one dose of 0.5 ml.

The applicant justified that there are no changes in terms of design, safety and performance characteristics, intended use, usability, and instructions for use regarding the medical device used in currently authorised quadrivalent vaccine, and in agreement with the European Commission, a Notified Body Opinion waiver requested by the applicant was accepted in this exceptional case.

2.3.2. Active Substance

2.3.2.1. General information

The active substance (AS) is a sterile suspension containing the purified outer membrane proteins, haemagglutinin (HA) and neuraminidase (NA) antigens from three influenza virus strains recommended every year by the WHO/CHMP/CBER/CDC and CHMP for the Northern Hemisphere: one influenza A (H1N1) virus, one influenza A (H3N2) virus and one influenza B virus from the Victoria lineage. Although there are actually three active substances from each of the three influenza strains, they are collectively referred to as the active substance in this report. Traces of viral envelope parts may be present in the product.

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 three strains used in the seasonal influenza vaccine consist of one influenza A (H1N1) virus, one influenza A (H3N2) virus, and an influenza B virus. 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 consists of three separate inactivated subunit influenza virus antigen concentrates. The influenza virus strains are individually grown in embryonated chicken eggs (each referred to as a monovalent pooled harvest (MPH)) and inactivated before purification of the surface antigens and formulation with the MF59C.1 adjuvant into a sterile suspension using the same process as for the approved product Fluad Tetra, adjuvanted quadrivalent influenza vaccine (aQIV). The MPH from each of the three selected viral strains is combined to produce the trivalent bulk product.

2.3.2.2. Manufacture, characterisation and process controls

The three ASs are produced and tested by Seqirus Vaccines Ltd, Liverpool. A QP declaration concerning GMP compliance by Seqirus Vaccines Liverpool is provided. All manufacturing sites involved in active substance manufacture and testing as appropriately GMP authorised.

Description of manufacturing process and process controls

The manufacturing process of active substances has been adequately described. 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. The main steps are inoculation of embryonated chicken eggs with a virus inoculum prepared from the working seed (WS). The eggs are then incubated at 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.

Inactivated allantoic fluid is concentrated and purified. 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). The surface antigens are then solubilised using polysorbate 80 and the antigens split from the virus core using cetyltrimethylammonium bromide (CTAB). The residual sub-viral particles and residual CTAB are removed. Then, a stabilizing solution is added to the subunit supernatant pool which is sterile filtered to produce the monovalent pooled harvest AS.

Alternatively, select strains may undergo an alternative pathway in which they are concentrated via an ultrafiltration/diafiltration step, followed by filtration. The resulting concentrated sterile-filtered monovalent pooled harvest is stored at 2-8°C until formulation.

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).

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 ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance manufacturing process is considered acceptable.

The batch size for the production of a single monovalent bulk is determined by the number of harvested production eggs. Therefore, the resulting number of vaccine doses is dependent upon the HA concentration of the individual monovalent bulk lots.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. 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 and includes specified-pathogen-free (SPF) embryonated eggs (manufacture of master and working seeds), production eggs (manufacture of influenza vaccine), influenza seed/virus reference strains, and master/working seed virus.

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. The applicant states that the suppliers have in place a documented programme for the veterinary and sanitary management of the flocks.

Example certificates of analysis (CoA) for each of the vendor-supplied materials are provided. All non-compendial ingredients are tested (either by the vendor or in-house) to ensure compliance with their

specification. In-coming materials are, at a minimum, tested for identity prior to release into production. The required testing requirements are indicated. 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; however, in these circumstances their infectivity titre would be retested to assess if an adjustment in the WS dilution in production is required.

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.

Filtration will be routinely performed unless particular strain characteristics preclude filtration.

The provided information on the starting materials is considered appropriate.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

Validation reports of the entire MPH manufacturing process, together with shipping studies were submitted. 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 procedure. 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 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.

The active substance manufacturing process has been validated adequately. Consistency in production has been shown on full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces the active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

The AS manufacturing process for aQIV has been developed based upon that of the trivalent products TIV (Agrippal)/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 site which is now known as Seqirus, 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 the pre sterile-filtration stage was transferred from Seqirus' predecessor's sites in Italy to the Seqirus, Liverpool site 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. All changes are considered acceptable and clearly justified.

Moreover, additional changes have been introduced in the AS manufacturing process following the initial approval of the aQIV. Those changes are well described and are considered acceptable and clearly justified.

Characterisation

The AS for each of the three 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 for the Northern Hemisphere.

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 neutralizing antibody.

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

Seqirus performs HA and NA characterisation studies on the first three lots of each new influenza strain used to confirm the identity, purity, and suitability of the two antigens, including SRID (Single Radial Immunodiffusion) measurements, SDS-PAGE (Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis) and NA identity as part of product release testing for each monovalent bulk harvest.

Extended characterisation testing as outlined under the EMA Guideline on Influenza Vaccines, Quality Module (EMA/CHMP/BWP/310834/2012) is performed and found acceptable.

The impurities of MPH have been sufficiently characterised. Impurities were classified as process-related impurities (ovalbumin, bioburden, endotoxin, formaldehyde, polysorbate 80, CTAB, sodium citrate, antibiotics and hydrocortisone) and product-related impurities (for which adequate control is described).

The active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods. The analytical results revealing that the active substance is consistent with the proposed structure. Stated impurities have been present in marketed aTIV and aQIV product over many years.

Furthermore, heterogeneity of the active substance was adequately characterised.

In summary, the characterisation is considered appropriate for this type of molecule.

2.3.2.3. Specification

The specifications for all MPHs include general tests (appearance), identity tests (haemagglutinin identity and content, neuraminidase identity), and tests for purity (viral inactivation, sterility, non-HA protein, endotoxin, process related impurities).

The active substance control strategy, including a specification for appearance and the IPC tests, are considered appropriate.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

The quality attributes (QAs) routinely tested at the level of the MPH are in line with the Ph.Eur. monograph on Influenza vaccines (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.

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 aTIV annual strain update submissions to document assay performance in support of the campaign product formulation.

Batch analysis data of several active substance batches were provided. The results are within the specifications and confirm consistency of the manufacturing process.

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 HA content of inactivated Influenza vaccines by the SRID test.

The antigen/antiserum reagents used during seasonal campaigns will be qualified, and the reagent qualification reports provided.

Information on reference materials is considered appropriate.

Container closure

The container closure system used during routine manufacture of the MPH is Bio-Process Containers (BPCs).

The information submitted is considered acceptable.

2.3.2.4. 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 programme 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.

2.3.3. Finished Medicinal Product

2.3.3.1. 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 composition of the aTIV finished product is the same as the previously EU-licensed Fluad Tetra (aQIV), except for the elimination of the influenza B/Yamagata strain.

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 aTIV finished product.

The formulation of the FP had been adapted to a quadrivalent (aQIV) presentation, derived from the previously EU-licensed trivalent vaccine Fluad. Now, the elimination of the B/Yamagata antigen from the formulation makes the vaccine trivalent again. aQIV has been licensed in the EU since 2020 and now, following WHO and EU recommendations, the antigens of the B/Yamagata strain are removed from the vaccine composition resulting in this new marketing authorisation application (MAA) for aTIV.

The manufacturing process and formulation of aTIV are similar to those of the registered adjuvanted aQIV, which was based on those registered for an earlier trivalent influenza vaccine. This previous trivalent influenza vaccine was registered in the EU in 1997 (as well as in many other countries worldwide, including US) for use in adults of 65 years of age and older. Although this trivalent vaccine has not been used in the EU since aQIV was approved, the trivalent vaccine has continued to be used in Canada.

Fluad trivalent contains a nominal amount of 45 µg of HA antigen per 0.5ml dose: 15 µg of haemagglutinin from each of the H1N1, H3N2 and B strains. The excipient concentration is the same as used in Fluad aTIV (including the MF59C.1 adjuvant). The excipients used for the aQIV formulation include: sodium chloride; potassium chloride; potassium dihydrogen phosphate; disodium phosphate dihydrate; magnesium chloride hexahydrate; calcium chloride dihydrate; MF59C.1 adjuvant (squalene, polysorbate 80, sorbitan trioleate, sodium citrate); water for injections. 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. There are no novel excipients used. An overfill of 0.1 mL is included to permit withdrawal of the nominal syringe volume (0.5 mL). An HA overage is also included (which is specific to a particular strain).

The batches used to perform clinical trials were manufactured in 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 Seqirus' predecessor's site in Italy site was performed to the commercial FP manufacturing site Seqirus Holly Springs (USA), where the batches relevant for the present MAA submission were manufactured. 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. Subsequent technical transfers of the formulation, filling, and packaging process from the Seqirus Holly Springs site to the formulation and filling sites listed in the dossier was performed. All relevant validation and comparability assessments were provided demonstrating the transfer has not affected the manufacturing process or quality of the finished product.

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 bulk adjuvant manufacture, 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 emulsification, is 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) and Seqirus Vaccines Ltd. (Liverpool, UK). The process validation parameters were within the respective normal operating ranges and met all acceptance criteria specified.

Batch analyses for several lots are presented (including validation/stability lots) produced at Seqirus Inc. (Holly Springs, US) and Seqirus Vaccines Ltd. (Liverpool, UK). All batches complied with the specifications approved at the time of release. Manufacture has also been appropriately validated. The shelf life of sterile MF59C.1 bulk adjuvant and storage conditions have been agreed in the dossier. 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 dossier, when the bulk adjuvant is stored in flex bags and protected from light. Additional long-term stability studies have been performed using flex bag containers from the approved vendor on the process validation batches. All parameters tested remained within specification. The available data support the proposed shelf-life and storage conditions.

In general, the information provided was acceptable.

Finished product container closure

The primary packaging is pre-filled syringes (type I glass) with a plunger stopper (bromobutyl rubber). The material complies with Ph. Eur. and EC requirements. aTIV can be presented in a single dose pre-filled Luer-lock syringe or a single dose pre-filled staked needle. Extractable and leachables studies as well as dose delivery studies were performed and found acceptable. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Concerning the microbiological attributes, the FP is a sterile solution, and no preservatives are used in the FP. Both formulation and filling of the syringes are carried out in controlled conditions, and the filled final product is tested for sterility.

2.3.3.2. Manufacture of the product and process controls

aTIV vaccine finished product manufacturing, packaging, testing and batch control sites are specified in the dossier. The finished product will be released by Seqirus Netherlands B.V., Amsterdam, the Netherlands.

The composition of the aTIV finished product is equivalent to that of aQIV, except for the deletion of the B/Yamagata antigen.

The manufacturing process and formulation of aTIV are similar to those of the registered adjuvanted aQIV, which was based on those registered for an earlier trivalent influenza vaccine.

The batch formula for the aTIV FP depends on the HA content of the monovalent bulk. The HA antigen content of each strain varies from lot to lot. Therefore, based on the HA concentration (potency) of

each monovalent bulk, the weight of HA antigen for each of three strains is calculated and the amount of the other FP components are adjusted according to a defined quantitative formulation.

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

Formulation involves the addition of the required three strains of antigen, phosphate buffered saline (PBS), water for injection (WFI), a stabilising solution and MF59C.1 adjuvant to a formulation vessel which is 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.

The applicant has committed to submit a post-approval variation to the Fluad MA for the introduction of a point of use filtration including the PPQ results and the data package generated for Fluad Tetra. This point is included as a quality recommendation (recommendation 1).

aQIV validation data has been presented in support of some of the process changes in the dossier. The aTIV and aQIV FPs have the same product composition and same appearance with the exception of an additional monovalent B strain in the aQIV vaccine. aTIV and aQIV are comparable and the number of monovalent strains has no impact on product characteristics, stability and critical quality attributes (CQAs). Since the product characteristics, stability and CQAs are the same between aTIV and aQIV, the aQIV validation data are considered applicable to aTIV as well. Numerous validation and qualification reports are provided. No new reports are provided compared to those previously evaluated for aQIV. The manufacturing process is considered validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

2.3.3.3. Product specification

The specifications proposed for release of the final trivalent bulk vaccine contains appropriate tests for identity (appearance, haemagglutinin identity for each of the 3 strains, squalene identity), potency (haemagglutinin content for each of the 3 strains), purity (sterility, non-HA protein, ovalbumin, CTAB, absence of live virus, endotoxin), and physiochemical attributes (particle size, osmolality, pH).

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

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

Since aTIV and aQIV FP have the same product composition, with the exception of an additional monovalent B strain in the quadrivalent vaccine, the analysis results of several aQIV FP formulation and filling PPQ batches from the different manufacturing sites are included. This approach is considered acceptable.

In addition, batch analysis results for several formulated lots of aQIV containing the strains used in the Northern Hemisphere (NH) 23/24 season are provided.

Moreover, aTIV specific data from the most recent NH 2023/24 campaign filled at the Holly Springs site and manufactured for the Canadian market has been presented in this section. The batches comply with the specifications registered for the Canadian aTIV market.

Reference materials

Information on the reference materials used for the active substance is applicable to the finished product.

2.3.3.4. Stability of the product

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

The stability studies for aQIV are aimed to support licensure and stability of the aTIV product, which is acceptable.

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 also sufficiently substantiated.

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 programme at the intended storage condition of 5 ± 3°C, as well as at least one lot under accelerated and stressed conditions.

Based on the available stability data (accelerated conditions at 25°C - 37°C for 6 weeks), it appears that the final vaccine remains relatively stable or shows only minimal loss of potency for at least a limited period of time. Therefore, the applicant is requested to provide guidance for users in section 6.4 of the SmPC (in line with EMA guideline EMA/CHMP/BWP/133540/2017), more particularly that short, accidental, temporary temperature excursions at room temperature (25°C) do not impact the vaccine's quality. The following statement could be considered (the applicant should propose and

justify a maximum exposure time (hrs/days) at 25°C): "Unopened Fluad Vaccine is stable for a total of xx hours/days at 25°C. It is not a recommended storage or shipping condition but may guide decisions for use in case of temporary temperature excursions during the storage at 2-8°C". This point is included as a quality recommendation (recommendation 2).

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

2.3.3.5. Adventitious agents

In addition to inactivation of influenza virus, the European Pharmacopoeia (Ph. Eur.) requires that the inactivation process be shown to be capable of inactivating avian leucosis viruses and mycoplasma.

Studies have been carried out to evaluate the effectiveness of the antigen production process to inactivate potential viral, bacterial and mycoplasma contamination in addition to influenza viruses.

The results from these studies are presented in section 3.2.A.2 Adventitious Agents Safety Evaluation.

The following information is detailed in 3.2.A.2 Adventitious Agents Safety Evaluation: Validation of virus removal and inactivation; Viral clearance studies; Validation of mycoplasma removal and inactivation; Risk assessment; TSE assessment; Virological control tests during the production process; and SPF and Production Egg Suppliers and Requirements/Specifications for Flocks and Eggs.

The information provided on adventitious agents is considered acceptable.

A risk assessment for adventitious agents in candidate virus vaccine (CVV) manufacturing is provided and considered acceptable.

With regards to TSE, the only animal derived materials identified are the eggs and the squalene from the adjuvant. Both are considered no to pose any risk of TSE. This is accepted.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Fluad (TIV) is a seasonal surface antigen inactivated influenza vaccine, adjuvanted with MF59C.1. The vaccine is provided in a glass pre-filled syringe containing 0.5 ml sterile suspension for injection for active immunisation of adults of 50 years of age and older.

Fluad contains predominantly purified HA and NA surface antigens from each of the three influenza virus strains, type A (H1N1 and H3N2) and type B (Victoria lineage), recommended annually for immunisation by the World Health Organisation (WHO) and the CHMP. The Influenza virus strains are individually grown in embryonated chicken eggs and inactivated before purification of the surface antigens and formulation with the MF59C.1 adjuvant. The MF59C.1 adjuvant is an oil-in-water emulsion composed of squalene, with the surfactants polysorbate 80 and sorbitan trioleate, in a citrate buffer.

aTIV contains a nominal total of 45 µg of antigens per 0.5ml dose; 15 µg of hemagglutinin per 0.5 ml dose from each of the A/H1N1, A/H3N2, and B/Victoria strains.

The aTIV FP is equivalent in composition to the aQIV FP (Fluad tetra), which has been licensed in the EU since 2020 except for the elimination of the B/Yamagata antigen. Before the aQIV approval, a trivalent version of the vaccine (aTIV, Fluad) was licensed in the EU (as well as in many other countries worldwide) since 1997. In Canada, the aTIV Fluad has continued to be marketed.

Other than the elimination of the B/ B antigen, there were no changes in the manufacturing process between the established commercial aQIV FP and the new aTIV FP. Thus, the assessment of the manufacture and control of the DS and DP have been in general straightforward.

aQIV manufacturing validation data has been presented in support of the current MAA for aTIV. Since the product characteristics, stability and CQAs are the same between aTIV and aQIV, the aQIV validation data are considered applicable to aTIV as well.

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

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to point of use filtration (quality recommendation 1) and in use conditions (quality recommendation 2). These points are included as recommendations for future quality development.

2.3.5. 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.

2.3.6. Recommendations for future quality development

Recommendation 01

The company has committed to submit a post-approval variation to Fluad for the introduction of a point of use filtration including the PPQ results and the data package generated for Fluad Tetra.

Recommendation 02

Based on the available stability data (accelerated conditions), it appears that the final vaccine remains relatively stable or shows only minimal loss of potency for at least a limited period of time. Therefore, the applicant is requested to provide guidance for users in section 6.4 of the SmPC (in line with EMA guideline EMA/CHMP/BWP/133540/2017), more particularly that short, accidental, temporary temperature excursions at room temperature (25°C) do not impact the vaccine's quality. The following statement could be considered (the applicant should propose and justify a maximum exposure time (hrs/days) at 25°C): "Unopened Fluad Vaccine is stable for a total of xx hours/days at 25°C. It is not a recommended storage or shipping condition but may guide decisions for use in case of temporary temperature excursions during the storage at 2-8°C".

2.4. Non-clinical aspects

2.4.1. Introduction

Non-clinical studies performed with aTIV include non-GLP immunogenicity (mice and rabbits) and challenge studies (mice), and GLP repeat dose toxicity (rabbits), reproductive and developmental toxicity (rabbits) and delayed contact hypersensitivity (Guinea pigs).

Supportive immunogenicity data are provided by non-GLP studies in ferrets with monovalent (H5N1) adjuvated pandemic formulations (aMIV); these studies are summarised in the Aflunov (zoonotic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted), EMEA/H/C/002094) Summary of

Product Characteristics (Seqirus, 2017). In addition, GLP non-clinical studies performed to characterise MF59 adjuvant have been completed.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The non-clinical pharmacology programme of aTIV was designed to address immunogenicity and protection from challenge. The pre-clinical programme 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.

Some studies were conducted to compare aTIV and aQIV. aQIV (Fluad Tetra/Quad/Quadrivalent) is the quadrivalent version of the Seqirus trivalent vaccine Fluad. The manufacturing process and formulation of aTIV and aQIV are the same, with the exception of an additional B strain included in aQIV.

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.

In vivo antibody-dose response and challenge studies were conducted with TIV with and without MF59 adjuvant, by intramuscular (clinical administration route) or subcutaneous administration in BALB/c mice, with additional immunogenicity endpoints included in the rabbit toxicology study. These species are commonly used for immunogenicity testing of vaccines. Mice were treated with a fraction of the human dose. This is acceptable considering the size of the animals.

Immunogenicity studies showed that TIV, alone or in combination with MF59 (aTIV), elicits a dose-related antigen-specific antibody response, even in seropositive mice. Proliferation of spleen-derived lymphocytes was also associated with immunisation. The presence of the adjuvant MF59 significantly increased the immune response, in both young and old mice.

In the challenge studies, mice were vaccinated before inoculation with wild type influenza virus. Immunised mice showed reduction in lung viral load and protection against challenge with lethal doses of influenza virus up to 200 days post-vaccination. No challenge study was conducted in ferrets with aTIV or TIV.

Although BALB/c mice are considered to exhibit a Th2-predominant immune response, this bias does not entail an issue for the non-clinical characterisation of the product as it is well described in the literature.

Immunogenicity was also evaluated (non-GLP) in rabbits during the GLP toxicology studies. In these studies, animals received two or three full human doses of either aTIV or a formulation equivalent to aQIV. Doses were administered intramuscularly two weeks apart. Antigen-specific antibodies were detected in all treated animals after the first vaccine dose. In the reproductive and developmental toxicity study in rabbits (Study No. AB09779), female rabbits received 4 doses of aTIV (twice before mating and twice during gestation). Hemagglutination inhibition (HI) titres were detected in aTIV-treated 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 MF59 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.

2.4.2.2. Secondary pharmacodynamic studies

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

2.4.2.3. Safety pharmacology programme

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

2.4.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted, which is in accordance with applicable guidelines.

2.4.3. Pharmacokinetics

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

Distribution and clearance studies of the adjuvant MF59 in mice and rabbits do not raise any specific safety concern.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

No single dose toxicity studies were performed by the applicant, which is in accordance with applicable guidelines.

2.4.4.2. Repeat dose toxicity

GLP toxicology studies were conducted with TIV and aTIV administered two or three times to rabbits. The maximum anticipated clinical vaccine dose was administered to the animals (45 µg HA (15 µg HA from each of the three virus strains) in 0.5 mL)).

The non-pivotal 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.

In pivotal study 488182 the rabbits received saline, Fluad (aTIV), Fluad High B (aQIV equivalent) and Fluad High (H3+IC31, IC31 is an adjuvant containing 500 nmol peptide (KLK) and 20 nmol oligodeoxynucleotide (ODN1a) in PBS buffer) influenza vaccine formulations by 3 intramuscular

injections. Rabbits received 3 intramuscular injections of aTIV containing a total of 45 µg of HA and a formulation containing a total of 60 µg of HA. aTIV and the aQIV equivalent formulation were administered using the clinical route and dose volume, and contained the maximum anticipated clinical dose of both antigen and adjuvant. In this study, there were no notable differences in local and systemic effects following administration of either vaccine. The vaccine formulations were immunogenic and well tolerated locally and systemically. The effects observed in the injection site and local lymph nodes are compatible with the expected effects of vaccination.

2.4.4.3. Genotoxicity

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

2.4.4.4. Carcinogenicity

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

2.4.4.5. Reproductive and developmental 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. No maternal or embryofoetal toxicity, teratogenicity or effects on post-natal development were observed.

2.4.4.6. Local tolerance

The local tolerance 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.

2.4.4.7. Other toxicity studies

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 sensitiser.

A package of GLP toxicity studies were conducted with the adjuvant MF59. No safety issues were detected. In addition, 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 indications proposed for Fluad, such as Fluad Tetra.

2.4.1. Ecotoxicity/environmental risk assessment

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

2.4.2. Discussion on non-clinical aspects

The primary pharmacodynamics of aTIV 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 aTIV and are considered not necessary in accordance with the Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014).

The toxicology of aTIV 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 support of other vaccines that have the same manufacturing process and adjuvant. Data derived from aQIV are considered directly relevant to aTIV because although aTIV contains less antigen, the same active substance is used in both vaccines, both vaccines contain the same amount of MF59C.1, and the manufacturing process is similar. In the assessment of aQIV (Fluad Tetra EMEA/H/C/004993/0000) it was confirmed that the addition of an additional antigen did not result in a significant change in the pharmacology or toxicology of the product compared to aTIV.

2.4.3. Conclusion on the non-clinical aspects

The MAA of Fluad is approvable from a non-clinical point of view.

2.5. Clinical aspects

2.5.1. Introduction

The current application includes clinical evidence from studies that were part of the initial marketing authorisation application of Fluad Tetra (aQIV, EMEA/H/C/004993/0000) which was approved for use in individuals 65 years of age and older and supportive studies that were part of an earlier clinical development in aTIV that was authorised in several EU member states through the MRP under the name of Chiromas/Fluad before the development of aQIV. It also includes a study which was submitted post-authorisation and that supported the extension of indication to individuals from 50 years of age (EMEA/H/C/004993/II/0043). No new clinical data have been submitted in this MAA. All relevant clinical studies have been previously submitted and reviewed as part of previous aQIV filings with EMA.

The initial MAA of Fluad Tetra included studies intended to support two distinct indications in two age groups:

"*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"

After the assessment of the clinical studies presented in the aQIV dossier, only the indication for older adults aged 65 years of age or older was granted. The applicant withdrew the MAA for the paediatric indication before CHMP opinion.

The indication for elderly subjects (65 years of age and over) was granted on May 2020. The extension of indication for subjects 50 to 64 years of age was granted in January 2024.

The indication that the applicant is seeking in this MAA for aTIV is for prophylaxis against influenza in adults of 50 years of age and older.

The paediatric studies have been included for consistency with the initial MAA dossier, but a paediatric indication is not sought by the applicant in this MAA. The paediatric data submitted is aiming to support the information on paediatric population in the SmPC. In fact, the PDCO has granted a product-specific waiver for all the paediatric age, from birth to less than 18 years of age.

GCP aspects

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

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

- **Tabular overview of main clinical studies**

Study No, Influenza Season, No. of Centres, Country	**Study Objectives**	**Study Phase, Study Design, Study Population**	**Test Products, No of Subjects: Enrolled / Exposed / Completed**	**Study Duration, Study Dates (FSFV, LSLV), Link to Synopsis**
V118_20 2017/2018 NH 20 centres United States	Safety and immunogenicity of aQIV vs. aTIV-1(Fluad) and aTIV-2 (containing the alternate B strain)	Phase 3 Randomised, Double Blind, Controlled, Clinical Study Adults ≥65 years of age	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 CSR V118_20 Synopsis
V118_18 2016/2017 NH 2017 SH 89 centres Bulgaria Colombia Czech Republic Estonia Latvia Lithuania Malaysia Philippines Poland Romania Thailand Turkey	Efficacy, Safety and Immunogenicity of aQIV vs Non-influenza Vaccine Comparator	Phase 3 Randomised, Observer-Blind, Controlled, Multicentre Clinical Study Adults ≥65 years of age	aQIV: 3394/3379/3263 Comparator: 3396/3382/3273	Duration: 12 months following a single vaccination Dates: 30 September 2016 to 23 July 2018 CSR V118_18 Synopsis
V70_27 2010/2011 NH 2011 SH 38 centres Colombia Panama The Philippines United States	Lot to lot consistency of aTIV; and safety, tolerability, immunogenicity of aTIV vs. TIV	Phase 3 Randomised, Controlled, Observer-Blind, Clinical Study Adults ≥65 years of age	aTIV: 3552 / 3541 / 3361 TIV (Agriflu): 3552 / 3541 / 3356	Duration: 12 months following a single vaccination Dates: 13 AUG 2010 to 16 NOV 2011 CSR V70_27 Synopsis

V118_23 6 centres in Estonia centres in Germany centres in the United States	Immunogenicity and safety	Phase 3, Randomised, Comparator controlled, Observer blind study	aQIV: MF59-adjuvanted egg-derived subunit inactivated quadrivalent influenza virus vaccine. QIV (comparator vaccine): Nonadjuvanted egg-derived split inactivated quadrivalent influenza virus vaccine (Fluarix Tetra/Quadrivalent). Healthy or with comorbidities that increase their risk of complications from influenza infection 50 to 64 years of age aQIV: 1027 subjects QIV: 1017 subjects 57.8 (50-64) years 794 M/1250 F	Sep-2021 Sep-2022 V118_23 CSR V118_23 CSR Synopsis

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Pharmacokinetic studies were not conducted in the development programme of aQIV and aTIV, in line with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev.1). Pharmacokinetic studies are not required for influenza vaccines as the kinetics properties of vaccines do not provide useful information for establishing adequate dosing recommendations.

2.5.2.2. Pharmacodynamics

Mechanism of action

Fluad provides active immunisation against three influenza virus strains (two A subtypes and one B type) contained in the vaccine. Fluad 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/164653/05 Rev. 1).

Specific levels of hemagglutination inhibition (HI) antibody titres post-vaccination with inactivated influenza vaccine have not been correlated with protection from influenza virus, but the HI antibody titres 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 contains the adjuvant MF59C.1 (MF59), which is designed to increase the antigen-specific immune response and to extend the duration of the immune response.

Primary and Secondary pharmacology

Consistent with the established routine for influenza vaccines, key immunological responses in the pivotal and supportive studies were assessed at baseline (i.e., prevaccination) and approximately 3 weeks post-vaccination, when the HA antibodies are at their highest levels in humans (Kunzel 1996). All serum samples collected from subjects were assayed for HI antibodies according to standard methods (Palmer 1975; Kendal 1982).

Studies of influenza infection, including human challenge studies in healthy adults, have indicated that HI antibody titres of 1:40 or greater have been associated with protection from influenza illness in up to 50% of subjects (Hobson et al. 1972; Hannoun et al. 2004).

The basis of the HI assay is that antibodies to the influenza virus that are present in the serum sample will prevent attachment of the virus to red blood cells. The binding of the viral HA surface protein to specific receptors on the membrane of red blood cells is called hemagglutination. Specific anti-HA antibodies present in human sera are able to neutralise the challenge virus in the assay and therefore inhibit the agglutination of the red blood cells.

The different immunogenicity HI assays performed are for homologous strains, heterologous strains, persistence of immune response and immune response upon revaccination.

Immunogenicity assessments were conducted by qualified and certified laboratories using validated assays.

Table 1 presents a comparison of the CBER criteria (CBER 2007) and former CHMP criteria (CPMP/BWP/214/96) for influenza vaccines. To meet CBER criteria, the lower limit of the 2-sided 95% CI of the immunogenicity endpoint must meet or exceed the pre-specified margin; the former CHMP criteria (CPMP/BWP/214/96) are based on the point estimate values for the immunogenicity endpoints.

For the main clinical studies included the efficacy section with primary objective of immunogenicity, the following immunogenicity criteria were applied:

- aQIV study V118_20 was designed to evaluate immunogenicity of aQIV versus aTIV-1 and aTIV-2 according to criteria established by CBER as a co-primary objective.
- aTIV study V70_27 was designed to evaluate immunogenicity of aTIV versus TIV according to criteria established by CBER as a co-primary objective. Study V70_27 also evaluated immunogenicity of aTIV according to former criteria established by the CHMP which was applicable at the time of study conduct as a third co-primary objective.

Table 1: CBER and CHMP criteria for evaluation of adequate immune response after influenza

vaccines

Endpoint	HI Titer Result	CHMP Criterion	CBER Criterion
GMR	N/A	> 2.0	N/A
HI Titer ≥ 1:40	Titer ≥ 1:40	> 60% of subjects	Lower bound of 2-sided 95% CI ≥ 60%
SCR	Negative (< 1:10) at prevaccination AND postvaccination titer ≥ 1:40; OR at least 4-fold titer increase if ≥ 1:10 at prevaccination	> 30% of subjects	Lower bound of 2-sided 95% CI ≥ 30%

Source: CPMP/BWP/214/96; CBER 2007

Abbreviations: GMR = geometric mean ratio; HI = hemagglutination; SCR = seroconversion rate

Notes:

The serological criteria presented are for HI antibody responses to meet CHMP Requirements in subjects >60 years of age and CBER requirements in subjects ≥65 years of age

Overall the assays performed to support the Immunogenicity assessment are considered adequate. The validation report provided in relation to the HI test performed by the different labs is considered adequate.

Assessment of immunogenicity in Study V118_23 followed guidance in Section III.B.1.a of the CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (CBER 2007).

All sera were tested by validated hemagglutination inhibition (HI) assays performed at one central laboratory. A validation report of the hemagglutination inhibition assay for the following influenza strains was provided: A/Victoria/2570/2019 (H1N1p2009); A/Cambodia/e0826360/2020 IVR-224 (H3N2); B/Victoria/705/2018 BVR-11 (B-Victoria lineage), and B/Phuket/3073/2013 BVR-1B (B-Yamagata lineage). The validation report of the analytical procedure for detecting antibody responses by hemagglutination inhibition assay (as described included assessment of precision, repeatability, intermediate precision, format variability, dilutional linearity/relative accuracy, and specificity. The HI assays were validated for use before clinical samples were tested.

Some of the studies included measured the immune response via microneutralisation (MN) assay and cell mediated response (CMI), although these were of exploratory nature. These are no further discussed in this report.

2.5.3. Discussion on clinical pharmacology

There are no dedicated pharmacokinetic (PK) studies submitted as part of this application. This is acceptable. The PK is not considered informative towards the determination of an optimal dose. Further, the metabolic pathways of vaccines are generally understood. Therefore PK studies are generally not required for vaccines. The CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005). states that in some cases PK evaluation is needed in particular when vaccines contain novel adjuvants/excipients. As MF59C.1 is a known adjuvant. It is also included in several centrally authorised influenza vaccines, such as Fluad Tetra (influenza vaccine (surface antigen, inactivated, adjuvanted)), Aflunov (zoonotic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)), Celldemic (Zoonotic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted, prepared in cell cultures)), Zoonotic Influenza Vaccine Seqirus (Zoonotic

influenza vaccine (H5N8) (surface antigen, inactivated, adjuvanted)) and Foclivia (Pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)). Additionally, it was also included in the composition of Focetria (influenza vaccine H1N1v (surface antigen, inactivated, adjuvanted)) as well as in the MF59C.1 adjuvanted trivalent inactivated seasonal vaccine Fluad which has been authorised throughout Europe since 1997.

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/164653/05 Rev. 1). Immunogenicity, as a surrogate measure for efficacy, determined by a validated HI assay, was assessed in all aQIV and aTIV clinical studies included in the application and results are described in detail in the sections on clinical efficacy. Overall the assays performed to support the Immunogenicity assessment are considered adequate. The validation report provided in relation to the HI test performed by the different labs is considered adequate. The use of serological surrogates as an approximation for vaccine efficacy is generally recognised by the CHMP.

2.5.4. Conclusions on clinical pharmacology

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

2.5.5. Clinical efficacy

The current application includes clinical evidence from studies that were part of the submission package of the MAA of Fluad Tetra (aQIV) and supportive studies that were part of an earlier clinical development in aTIV that was authorised in several EU member states through the MRP under the name of Chiromas/Fluad. It also includes a study which was submitted post authorisation and that supported the EoI to subjects aged 50 years of age and above. No new clinical data has been submitted in this MAA.

Although the clinical package in the initial MAA for aQIV contained studies carried out in the paediatric population with the intention to obtain an indication in children, after the assessment of the paediatric data, the applicant withdrew the paediatric indication. The main studies that support the indication in adults are: V70_27, V118_20, V118_18 and V118_23. Other supportive studies have been submitted.

The studies in children have been included in this report for consistency with the initial dossier, but there is no claim for an indication in children. The paediatric data submitted is aiming to support the information on paediatric population in the SmPC.

2.5.5.1. Dose response studies

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, most adverse events were mild or moderate. Therefore these studies support the current proposed dose of antigen and adjuvant.

2.5.5.2. Main studies

V70_27: A Phase 3, Randomised, 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.

Main inclusion criteria

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

Main 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 non-inferiority 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 report).

Main secondary objectives

To evaluate the superiority of aTIV compared to TIV with regards to at least 2 heterologous strains and to demonstrate the non-inferiority 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 post-vaccination 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 and Blinding (masking)**

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.

The administration of the vaccines was performed by an unblinded designated person. All other personnel were 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.

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 analysis is 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 randomised and vaccinated, and 6,717 subjects (94%) completed the study (95%). 3,552 were randomised and 3,541 vaccinated in the aTIV group. 3,552 were randomised and 3,541 vaccinated in the aTIV group.

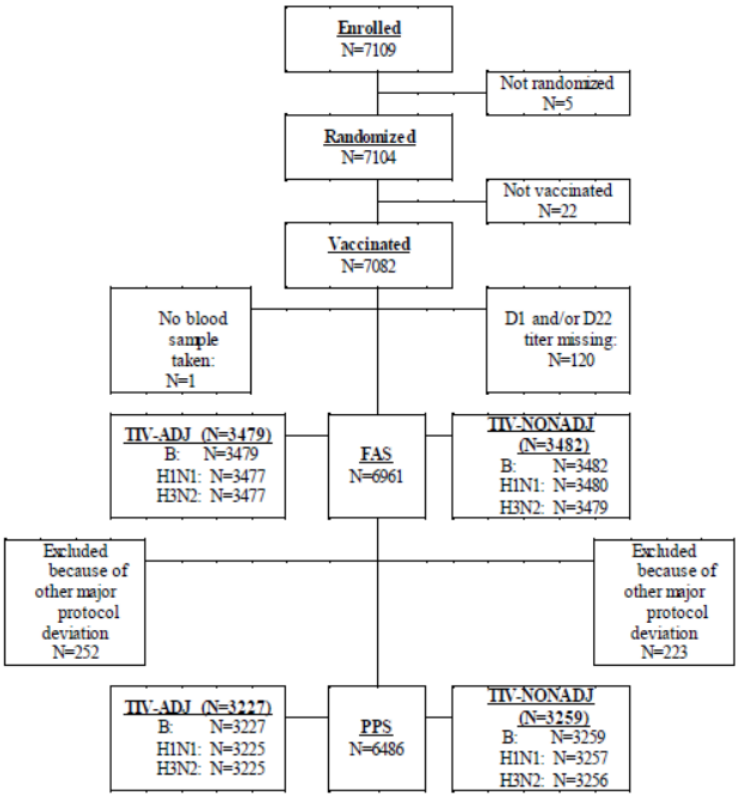


Figure 1: Participant flow

- **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 the 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 randomised subjects in the day 22 FAS were high-risk; most of these subjects were included in the day 22 PPS (34% of randomised subjects; n=2,385).

Table 2: 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**

Superiority of immunologic response of pooled aTIV when compared with TIV was analysed using the day 22 FAS. Of all randomised and vaccinated subjects, 6,961 (98%) were included in the FAS for homologous strains. The non-inferiority of pooled lots of aTIV when compared with TIV was analysed using the day 22 PPS. Of all randomised and vaccinated subjects, 6,486 (91%) were included in the PPS for homologous strains.

As per protocol, 1,768 subjects (25% of randomised 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 randomised subjects).

Persistence against homologous and heterologous strains was assessed in the antibody persistence subset (380 subjects).

Baseline characteristics of the FAS immunogenicity are in line with the overall enrolled population.

- **Outcomes and estimation**

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 3: 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)	<0.0001	0.998	<0.001	1.000
	Day 22[c] (95% CI)	98 (92-104)	71 (67-76)	1.37 (1.29-1.46)				
	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)	<0.0001	0.011	<0.001	0.055
	Day 22[c] (95% CI)	267 (253-282)	167 (158-176)	**1.6 (1.51-1.68)**				
	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)	<0.0001	1.000	<0.001	1.000
	Day 22[c] (95% CI)	27 (26-29)	24 (23-25)	1.14 (1.08-1.2)				
	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.

Day 1 and day 22 GMTs and day 22/day 1 GMRs using the PPS were similar to those seen using the FAS. The lower bound of the 95% CI for the day 22 vaccine group GMT ratios for all 3 homologous strains was >0.67, thereby establishing non-inferiority of *a*TIV to TIV against homologous strains. The difference in response between the *a*TIV and TIV groups was most pronounced for the A/H3N2 strain.

Table 4: Geometric mean HI titres (95% CI) and vaccine group ratios against homologous strains: day 22 PPS

		TIV-ADJ	TIV-NONADJ	TIV-ADJ : TIV-NONADJ
A/California/7/2009-like (H1N1)		**N=3225**	**N=3257**	
	Day 1 (95% CI)	7.64 (7.2-8.11)	7.68 (7.23-8.14)	1 (0.94-1.05)
	Day 22[a] (95% CI)	99 (93-106)	70 (66-75)	**1.4 (1.32-1.49)**
	Day 22: Day 1 (95% CI)	14 (13-15)	9.77 (9.09-11)	1.41 (1.31-1.51)
A/Perth/16/2009-like (H3N2)		**N=3225**	**N=3256**	
	Day 1 (95% CI)	27 (25-29)	26 (24-28)	1.02 (0.94-1.1)
	Day 22[a] (95% CI)	272 (257-288)	169 (159-179)	**1.61 (1.52-1.7)**
	Day 22: Day 1 (95% CI)	10 (9.66-11)	6.59 (6.07-7.15)	1.59 (1.47-1.72)
B/Brisbane/60/2008-like		**N=3227**	**N=3259**	
	Day 1 (95% CI)	6.15 (5.88-6.43)	6.12 (5.85-6.4)	1 (0.96-1.05)
	Day 22[a] (95% CI)	28 (26-29)	24 (23-26)	**1.15 (1.08-1.21)**
	Day 22: Day 1 (95% CI)	4.96 (4.67-5.27)	4.34 (4.09-4.6)	1.14 (1.08-1.21)

Source: Table 14.2.1.1.4.
Bold: TIV-ADJ was noninferior to TIV-NONADJ based on day 22 GMT ratios.
Abbreviations: CI = confidence interval; GMT = geometric mean titer; HI = hemagglutination inhibition; PPS = per protocol set.
[a] Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ:TIV-NONADJ) are adjusted for baseline 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 5: 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) post-vaccination.

Table 6: 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%.

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 7). Results were similar considering the endpoint seroconversion (Table 8).

Table 7: 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 8: 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)	Day 22	N=2502	N=2529		N=975	N=951	
		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)	Day 22	N=2502	N=2528		N=975	N=951	
		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	Day 22	N=2504	N=2531		N=975	N=951	
		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%).

aTIV was non-inferior to TIV among high-risk subjects against all 3 homologous strains using the predefined requirements, i.e., the day 22 GMT ratio had a 95% CI with a lower bound >0.67 for the FAS/PPS. Although superiority was not achieved among high-risk subjects, statistically significantly higher GMTs for aTIV against the 2 homologous A strains compared with TIV were demonstrated.

Table 9: Geometric mean HI titres (95% CI) and vaccine group ratios in high-risk subjects against homologous strains: day 22 FAS

Table 11.4.1.2-3: Geometric Mean HI Titers (95% CI) and Vaccine Group Ratios in High-Risk Subjects Against Homologous Strains: Day 22 FAS

		TIV-ADJ	TIV-NONADJ	TIV-ADJ : TIV-NONADJ	Unadjusted p-value		Multiplicity-adjusted p-value	
					Difference	Superiority	Difference[b]	Superiority[c]
A/California/7/2009-like (H1N1)		N=1299	N=1273					
	Day 1	8.22 (7.51-9)	8.53 (7.79-9.35)	0.96 (0.87-1.06)				
	Day 22[a]	106 (97-116)	80 (73-88)	1.32 (1.2-1.45)	<0.0001	0.9953	<0.001	1.000
	Day 22: Day 1	12 (11-14)	9.17 (8.28-10)	1.35 (1.21-1.5)				
A/Perth/16/2009-like (H3N2)		N=1299	N=1273					
	Day 1	28 (25-31)	26 (24-29)	1.05 (0.94-1.18)				
	Day 22[a]	249 (230-270)	162 (149-175)	1.54 (1.42-1.68)	<0.0001	0.2688	<0.001	1.000
	Day 22: Day 1	9.27 (8.31-10)	6.24 (5.59-6.96)	1.49 (1.32-1.67)				
B/Brisbane/60/2008-like		N=1300	N=1273					
	Day 1	6.37 (5.96-6.81)	6.54 (6.12-7)	0.97 (0.91-1.05)				
	Day 22[a]	30 (28-32)	27 (25-29)	1.11 (1.03-1.21)	0.0076	1.0000	0.015	1.000
	Day 22: Day 1	4.48 (4.14-4.84)	3.98 (3.68-4.31)	1.12 (1.03-1.22)				

Source: Table 14.2.1.2.6; Appendix 16.1.9.1.6-2, Appendix 16.1.9.1.6-4.
Abbreviations: CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer; HI = hemagglutination inhibition.
[a] Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ:TIV-NONADJ) are adjusted for baseline titer, country, and age cohort.
[b] Difference: 2-sided p-value for testing whether the lower bound of the 95% CI for TIV-ADJ/TIV-NONADJ ratio is different from 1.0.
[c] Superiority: 1-sided p-value for testing whether TIV-ADJ/TIV-NONADJ ratio exceeds 1.5.

Table 10: Geometric mean HI titres (95% CI) and vaccine group ratios in high-risk subjects against homologous strains: day 22 PPS

		TIV-ADJ	TIV-NONADJ	TIV-ADJ : TIV-NONADJ
A/California/7/2009-like (H1N1)		N=1194	N=1190	
	Day 1	8.03 (7.3-8.84)	8.48 (7.7-9.33)	0.95 (0.86-1.05)
	Day 22[a]	110 (100-122)	80 (73-88)	**1.38 (1.25-1.52)**
	Day 22: Day 1	13 (12-15)	9.25 (8.31-10)	1.41 (1.27-1.58)
A/Perth/16/2009-like (H3N2)		N=1194	N=1190	
	Day 1	28 (25-31)	27 (24-30)	1.04 (0.92-1.17)
	Day 22[a]	260 (238-283)	165 (152-180)	**1.57 (1.44-1.72)**
	Day 22: Day 1	9.72 (8.64-11)	6.34 (5.64-7.13)	1.53 (1.36-1.73)
B/Brisbane/60/2008-like		N=1195	N=1190	
	Day 1	6.33 (5.89-6.79)	6.54 (6.09-7.02)	0.97 (0.9-1.04)
	Day 22[a]	30 (28-33)	27 (25-29)	**1.12 (1.03-1.22)**
	Day 22: Day 1	4.56 (4.19-4.95)	4.03 (3.71-4.38)	1.13 (1.04-1.23)

Source: Table 14.2.1.2.3.
Abbreviations: CI = confidence interval; GMT = geometric mean titer; HI = hemagglutination inhibition; PPS = per protocol set.
Bold: TIV-ADJ noninferior to TIV-NONADJ based on day 22 GMT ratios.
[a] Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ:TIV-NONADJ) are adjusted for baseline titer, country, and age cohort.

- **Summary of main efficacy results**

The following table 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 11: Summary of efficacy for trial V70_27

Title: A Phase 3, Randomised, 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	Randomised, 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 randomised: 3552, vaccinated 3541
	TIV (TIV-NONADJ, Aggripal)	A/California/7/2009 (H1N1)-like strain A/Perth/16/2009 (H3N2)-like strain B/Brisbane/60/2008-like strain number randomised: 3552, vaccinated 3541

Endpoints and definitions	Primary endpoint	**GMT ratio** (geometric mean titre) **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 titre) **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 titre) **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		

V118_20: Phase 3, Randomised, 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

Methods

- **Study Participants**

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 enrolment 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 enrolment 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). Enrolment could have been considered if fever was absent for 72 hours.
13. Signs or symptoms of acute infection at the time of screening. Enrolment 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 (Fluad Tetra):** 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 complaint 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 f or 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**

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 characterise 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. Characterisation of the immunogenicity of aQIV using other immunological assays (e.g., virus neutralisation [MN] or anti-neuraminidase antibody assays may be performed).

Note: Additional immunogenicity testing (e.g., virus neutralisation [microneutralisation]) 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**

The immunogenicity of study vaccines was assessed 21 days (i.e., on Day 22) after vaccine administration by measuring the HI antibody titres 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 titre (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 post-vaccination (Day 22) HI titre for aTIV-1 (or aTIV-2) over the geometric mean of post-vaccination (Day 22) HI titre for aQIV.*

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

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 titre ≥1:40

Success Criteria for Co-Primary Objectives

<u>To Demonstrate Noninferiority</u>

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

**GMR was defined as the geometric mean of the fold increases of post-vaccination antibody titre over the pre-vaccination antibody titre.*

For each treatment group and strain, summary tables were presented for GMT and 95% CIs, percentage of subjects with a titre ≥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 post-vaccination GMTs and SCR) were performed with adjustment for covariates including prevaccination titre, 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 randomised 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 (titre) 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 and Blinding (masking)**

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

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.

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 randomisation 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 randomised, 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 analysed "as randomised" (i.e., according to the vaccine the subject was randomised 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 analysed as "treated" (i.e., according to the vaccine a subject received rather than the vaccine to which the subject was randomised).

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 titres were performed on the logarithmically transformed (base 10) values. Individual HI titres 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 analysed separately.

To determine the GMT ratio (adjusted analysis), a general linear model (GLM) was fitted on log transformed (base ten) post-vaccination HI titre as the outcome variable and terms for covariates:

vaccine treatment, prevaccination HI titre, 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 analysed 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 titres and were completed by providing minimum, maximum and median titres for each vaccine group.

Binary data (i.e., percentages of subjects with seroconversion and with titre ≥1:40) were summarised 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 enrolment (≥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)

Results

- **Participant flow**

In total 1,778 subjects were enrolled and randomised 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%).

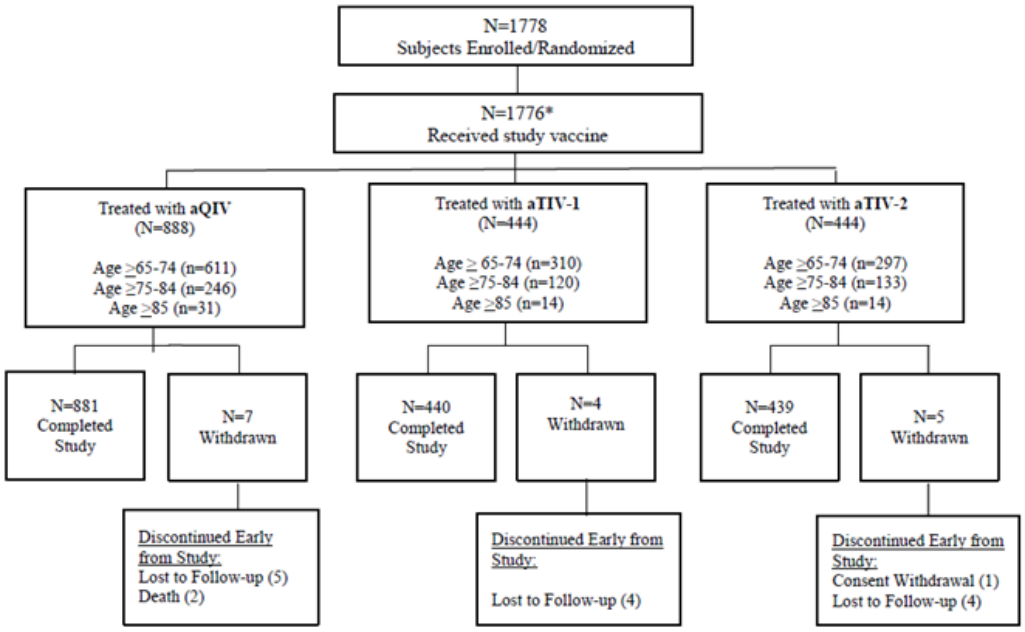


Figure 2. Of the total of 1778 subjects enrolled and randomized, a total of 1776 subjects were given study vaccination. A total of 1760 subjects completed the study. Reasons for early discontinuation from the study included withdrawal of consent (n=1), lost to follow-up (n=13), and death unrelated to 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

Figure 2: participant flow

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.

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.

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 hospitalisation due to pneumonia or influenza and death from any cause; however, subjects ≥75 years of age tended to be higher risk for influenza-related hospitalisations 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 hospitalisation and death from any cause; and most subjects had previous influenza vaccination.

Table 12: 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 randomised 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 randomised, 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 randomised, 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 randomised, with 59 (100%) receiving 1 vaccination of aQIV, aTIV, or aTIV-2, and 59 (100%) subjects included in both immunogenicity FAS and PPS.

- **Outcomes and estimation**

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 post-vaccination 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).

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

Geometric Mean Titre Ratios

Table 13 presents the post-vaccination HI antibody GMTs and analyses of non-inferiority of aQIV relative to aTIV for each strain 22 days post-vaccination in adults ≥65 years. These were for aQIV: 65.01 (95% CI: 57.79,73.13) for H1N1, 294.91 (95% CI: 261.88, 332.09) for H3N2, 24.67 (95% CI: 22.67, 26.84) for B/Yam and 30.78 (95% CI: 28.27, 33.51) for B/Victoria. For aTIV-1 and aTIV-2 the respective values were 75.16 (95% CI: 66.68, 84.72) for pooled H1N1, 293.31 (259.91, 330.99) for pooled H3N2, 24.30 (95% CI: 22.00, 26.84) for B/Yam for aTIV-2 and 30.13 (95% CI: 27.31, 33.24) for B/Vic for aTIV-1.

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 13: 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 (p er-Protocol Set)

Strain	Study groups				GMT ratio[a] (aTIV/aQIV) and 95% CI	Noninferiority[b] met?
	aQIV	aTIV-1	aTIV-2	aTIV pooled		
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 titre of <1:10 before vaccination achieving a HI antibody titre of ≥1:40 after vaccination, or with a HI titre of ≥1:10 before vaccination achieving a 4-fold or greater increase in HI titre after vaccination.

The table below presents seroconversion rates and analyses of noninferiority of aQIV relative to aTIVs for each strain 22 days post-vaccination 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 14: 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.

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 titre ≥1:40.

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

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 titre ≥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 15 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 titre ≥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 titre ≥1:40 were met for A strains, but not for B strains. The proportion of subjects with HI titre ≥1:40 against B strains in the aTIV-1 and aTIV-2 groups were similar (lower limits of the 95% CI below 60%).

Table 15: Immunogenicity as measured by percentages of subjects with HI titre >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 characterise 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 16: GMT and GMT ratio of HI antibody titres by vaccine group on day 22 - Analyses of superiority of aQIV relative to aTIV for the alternate B strain (FAS) – modified to reflect only B strains

Strain	Measure	aQIV vaccine (N=886)	aTIV-1 vaccine (N=443)	aTIV-2 vaccine (N=441)	aTIV-pooled (N=884) [b]
Adjusted Analysis*					
B-Yamagata Lineage	n	886	443	441	
	GMT (95% CI)	24.81 (22.80, 27.00)	15.92 (14.44, 17.55)	24.59 (22.27, 27.16)	
	GMT Ratio (95% CI) [a]		0.64 (0.58, 0.70)	0.99 (0.90, 1.09)	
B-Victoria Lineage	n	886	443	441	
	GMT (95% CI)	31.02 (28.50, 33.76)	30.22 (27.41, 33.33)	21.94 (19.87, 24.24)	
	GMT Ratio (95% CI) [a]		0.97 (0.89, 1.07)	0.71 (0.64, 0.78)	

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 is defined as the geometric mean of the post-vaccination (Day 22) HI titer for aTIV-1 and/or aTIV-2 divided by the geometric mean of post-vaccination (Day 22) HI titer for aQIV.
Note 3: n is the number of subjects with non-missing HI titer results at both pre- and post-vaccination;
Individual HI titers that were recorded as '<10' were taken as equal to 5.
Note 4: * Adjusted Model: Log-Transformed Post-Vaccination HI Titer = Vaccine Group [3 vaccines] + Age Group [>=65-74, >=75-84, and >=85 years] + Sex [male, female] + Vaccination History [y/n] + Log-transformed Pre-Vaccination HI Titer + Site.
Note 5: ** Unadjusted analysis model: Log-transformed Post-Vaccination HI Titer=Vaccine.
[a] Confidence intervals for the GMT ratio is calculated based on the normality assumption of log titers.
[b] aTIV-1 and aTIV-2 vaccine groups are pooled for the analysis of A-H1N1 and A-H3N2 strains. For B/Victoria TIV=TIV-1, for B/Yamagata TIV=TIV-2.

Data Source: Listing 16.2.6.1
Program Name: T-14-02-01-01-02.SAS
Table Generation: 07SEP2018 12:00

Table 17: SCR and SCR difference of HI antibody titres by vaccine group on day 22 - Analyses of superiority of aQIV relative to aTIV for the Alternate B strain (FAS) – modified to reflect only B strains

Strain	Measure	aQIV vaccine (N=886)	aTIV-1 vaccine (N=443)	aTIV-2 vaccine (N=441)	aTIV-pooled (N=884) [c]
B-Yamagata Lineage	SCR: n/M (%)	148/886 (16.70)	21/443 (4.74)	69/441 (15.65)	
	95% CI of SCR [a]	14.31, 19.33	2.96, 7.16	12.38, 19.38	
	SCR Difference (95% CI) [b]		-11.96 (-15.12, -8.81)	-1.06 (-5.24, 3.13)	
B-Victoria Lineage	SCR: n/M (%)	120/886 (13.54)	53/443 (11.96)	12/441 (2.72)	
	95% CI of SCR [a]	11.36, 15.98	9.09, 15.36	1.41, 4.70	
	SCR Difference (95% CI) [b]		-1.58 (-5.35, 2.19)	-10.82 (-13.54, -8.11)	

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) is defined as the percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer >= 1:40 or a pre-vaccination HI titer >= 1:10 and a >= 4-fold increase in post-vaccination 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.
The SCR Difference is defined as the difference between the SCR of post- vaccination (Day 22) HI titer for aTIV-1 (or aTIV-2) and the SCR of post-vaccination (Day 22) HI titer for aQIV, that is, SCRaTIV-SCRaQIV.
[a] The 95% CIs for SCR are the exact confidence intervals based upon the binomial distribution.
[b] The Asymptotic 95% CIs for the difference in SCRs between aTIV and aQIV.
[c] aTIV-1 and aTIV-2 vaccine groups are pooled for the analysis of A-H1N1 and A-H3N2 strains. For B/Victoria TIV=TIV-1, for B/Yamagata TIV=TIV-2.

Data Source: Listing 16.2.6.1
Program Name: T-14-02-02-01-02.SAS
Table Generation: 07SEP2018 12:00

Table 18: Analyses of superiority of aQIV relative to aTIV for the alternate B strain (FAS)

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 titre and geometric mean ratio

The PPS baseline GMTs were comparable between aQIV and aTIV groups. The GMR (post-vaccination/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).

Post-vaccination 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 post-vaccination 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 19: Seroconversion rates of HI antibody titres 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 titre ≥1:40 at day 1 and day 22

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

At Day 1 (prevaccination) in the PPS, the proportion of subjects with HI titres ≥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 post-vaccination, the proportion of subjects with HI titres ≥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 post-vaccination HI titres across vaccine groups. Post-vaccination HI titres 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 titre ≥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 post-vaccination, there were no notable differences in the proportion of subjects with HI titre ≥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 titre ≥1:40 against B-Yamagata appeared to be reduced with age. 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.

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 post-vaccination 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 20: Percentages of subjects with HI titre ≥1:40 and seroconversion rates at 22 days post-vaccination 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 analysed compared to male subjects (N=758). At day 22 post-vaccination the percentage of individuals who achieved HI titre ≥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 hospitalisation 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 titre ≥1:40 post-vaccination 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 post-vaccination proportion of subjects with HI titre ≥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 post-vaccination HI titres are comparable in these subgroups for A-H1N1 and A-H3N2 strains.

- **Summary of main efficacy results**

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

Table 21: Summary of efficacy for trial V118_20

Title: a Phase 3, Randomised, 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 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 randomised: 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 randomised: 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 randomised: 444
Endpoints and definitions	First Co-Primary endpoint	**GMT ratio** (geometric mean titre) **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 titres as GMTr and SCR difference on day 22
	Secondary endpoint	**GMT ratio** (geometric mean titre) **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 titres 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)	-	24.30 (22.00, 26.84)	
	B/Vic GMT D22 (95% CI)	30.78 (28.27, 33.51)	30.13 (27.31, 33.24)	-	
	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)	-	15.47 (12.20, 19.23)	
	B/Vic SCR (95%CI)	13.42 (11.22, 15.86)	12.16 (9.24, 15.60)	-	
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)	15.92 (14.44, 17.55)	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)
		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)

V118_18: Phase III, Randomised, Observer-Blind, Controlled, Multicentre 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

- **Study Participants**

Main inclusion criteria

Males and females ≥ 65 years old who are healthy or have co-morbidities.

Main exclusion criteria

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

Receipt of diphtheria or tetanus toxoid or pertussis (acellular or whole cell) vaccines within the previous 5 years.

- **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) titre 21 days after vaccination, against influenza strains homologous to the seasonal vaccine.

Exploratory Immunogenicity Objective:

6. To characterise the immunogenicity of aQIV using other immunological assays (such as microneutralisation [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 analysed using two ILI definitions for influenza. Below are found the primary efficacy endpoint.

<u>Primary Efficacy Endpoint</u>

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.

Two definitions of ILI were specified in the study protocol:

- Primary protocol-defined ILI: a presence of at least one respiratory symptom (sore throat, cough, sputum production, wheezing, or difficulty breathing) concurrently with at least one systemic symptom (temperature of > 37.2°C/99°F, chills, tiredness, headache, or myalgia).
- Modified Centres for Disease Control and Prevention (CDC) ILI definition: Fever (temperature f > 37.2°C/99°F) with cough or sore throat.

Immunogenicity endpoints

The measures of immunogenicity used for secondary objective 5 as determined by the HI assay against homologous strains at Days 1 and 22, included the following:

- Geometric mean titres (GMT) for HI.
- Geometric mean titres Ratios (GMRs) for HI at Day 22/Day 1.
- Percentages of subjects with an HI titre ≥ 1:40.
- Percentages of subjects who achieved seroconversion (defined as: HI ≥ 1:40 for subjects sero-negative at baseline [HI titre < 1:10]; or a minimum 4-fold increase in HI titre for subjects sero-positive at baseline [HI titre ≥ 1:10]) on Day 22.
- Reverse cumulative distributions of HI titres at Day 22.

The endpoints of percent of subjects achieving seroconversion and HI titre ≥ 1:40 at Day 22 was assessed against the criteria described in CBER Guidance Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (2007). Specifically, this was that:

- The lower limit (LL) of the two-sided 95% confidence interval (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 titre ≥ 1:40 should have met or exceeded 60%.

- **Sample size**

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

- **Randomisation and Blinding (masking)**

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

The trial is designed as an observer-blind study. The administration of the vaccines was performed by an unblinded designated person. Participants or the investigative site staff involved in the monitoring of conduct of the trial up until completion of the trial and final data review remain blinded, except in a medical emergency.

- **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 randomised 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 randomised, 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 randomised 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 analysed using the FAS Efficacy and PPS Efficacy sets. All non-key secondary VE objectives were analysed 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: VE estimates were calculated using similar analyses as the primary and secondary efficacy objectives.

Immunogenicity

Immunogenicity data were analysed using FAS Immunogenicity and repeated using PPS Immunogenicity if more than 5% of subjects were excluded from FAS Immunogenicity. All statistical analyses for HI titres were performed on the logarithmically (base 10) transformed values. Individual HI titres 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 titres and were completed by providing minimum, maximum and median titres for each vaccine group.

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

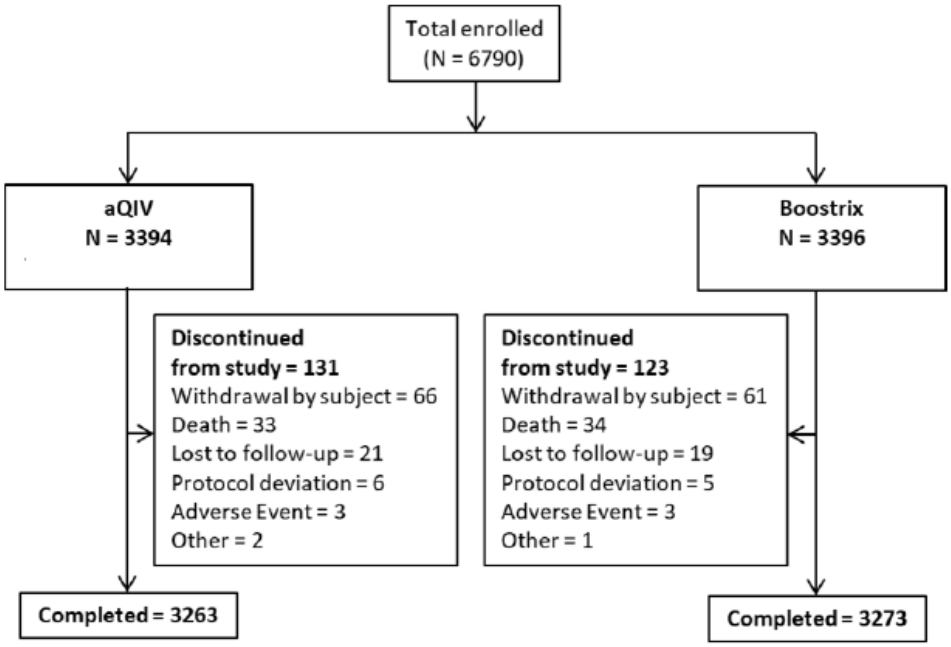
Immunogenicity endpoints at Day 22 were assessed according to the criteria for sufficient immune response described in Centre for Biologics Evaluation and Research (CBER) Guidance 'Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines' (2007) states the following:

- 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 titre ≥ 1:40 should have met or exceeded 60%.

Results

- **Participant flow**

Overall, 6,790 subjects were enrolled in this study (3,394 in the aQIV arm and 3,396 in the Boostrix arm). 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%]).



Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; N = number of subjects.
Source: Table 14.1.1.2

Figure 3: Participant flow

- **Recruitment**

This study was conducted between 30 September 2016 and 23 July 2018 at 89 sites in 12 countries: 1 1 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**

There were 4 protocol amendments during the study (from version 1.0 to version 5.0).

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.

The mean age (standard deviation; SD) was 71.9 (5.44) years and 71% of subjects were in the 65-74 year age group. More than half of the subjects were female (4194 [61.8%]). Nearly half of the subjects were White (3271 [48.2%]) and a third were Asian (2298 [33.8%]). A high proportion of subjects (4778 [70.4%]) had not received seasonal influenza vaccine in the past 5 years. 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.

Table 22: Demography and baseline characteristics - all enrolled set

	aQIV (N = 3394)	Boostrix (N = 3396)	Total (N = 6790)
Age (years)			
n	3394	3396	6790
Mean (SD)	71.9 (5.53)	71.8 (5.36)	71.9 (5.44)
Median	71.0	71.0	71.0
Age Group			
n	3394	3396	6790
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%)
Sex			
n	3394	3396	6790
Male	1289 (38.0%)	1307 (38.5%)	2596 (38.2%)
Female	2105 (62.0%)	2089 (61.5%)	4194 (61.8%)
Ethnic Origin			
n	3394	3396	6790
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%)
Race			
n	3394	3396	6790
American Indian or Alaska Native	62 (1.8%)	59 (1.7%)	121 (1.8%)
Asian	1139 (33.6%)	1159 (34.1%)	2298 (33.8%)
Black or African American	1 (0.0%)	0	1 (0.0%)
White	1642 (48.4%)	1629 (48.0%)	3271 (48.2%)
Other	550 (16.2%)	549 (16.2%)	1099 (16.2%)
Body Mass Index (kg/m^2)			
n	3391	3393	6784
Mean (SD)	27.05 (4.989)	26.96 (4.995)	27.00 (4.992)
Median	26.60	26.50	26.50
Previous Seasonal Influenza Vaccine in the Past 5 Years			
n	3394	3396	6790
Yes	991 (29.2%)	1021 (30.1%)	2012 (29.6%)
No	2403 (70.8%)	2375 (69.9%)	4778 (70.4%)
Comorbidity Score			
N	3394	3396	6790
< 50	2472 (72.8%)	2474 (72.9%)	4946 (72.8%)
≥ 50	922 (27.2%)	922 (27.1%)	1844 (27.2%)
Smoking Status			
n	3394	3396	6790
Smoking	325 (9.6%)	335 (9.9%)	660 (9.7%)
Not smoking	3069 (90.4%)	3061 (90.1%)	6130 (90.3%)

Abbreviations: aQIV = Adjuvanted Quadrivalent Influenza Vaccine; N= number of subjects; SD = standard deviation.
Note 1: Percentages are based on the number of subjects in each vaccine group.
Source: Table 14.1.1.3

- **Numbers analysed**

Overall, 6,761 subjects received study treatment according to the randomisation 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 and estimation**

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 23: 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
	B	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, 35 cases by B strains, 9 cases by A/H1N1 strain. 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 titre 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%.

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.

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.

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 24: 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 25: 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 26: 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

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: 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 27: 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 key secondary efficacy objective and for the other 3 secondary objectives 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 key secondary objectives nor any of the secondary objectives were met, as the LL of the 95% CI of VE estimates did not exceed 40%.

Similarly, neither the key secondary efficacy objective nor any of the three secondary objectives were met when the Protocol-defined ILI definition was used.

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, 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 28: 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.

Immunogenicity results

Geometric mean titres and Geometric mean titres Ratios for HI at Day 22/Day

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 Titres (GMT) and Geometric Mean Ratios (Day 22/Day 1) (GMR) results are presented in the following Table.

Table 29: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 with an HI Tier ≥ 1:40

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

- At Day 1, percentage of subjects with HI titres ≥ 1:40 were similar in both vaccine groups.
- At Day 22 post-vaccination, a significantly higher proportion of subjects in the aQIV group had reported HI antibody titre ≥ 1:40 compared to Boostrix group.
- The CBER criteria for sufficiency of immune response 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 titre ≥ 1:40 was > 60%).

Table 30: Number (%) of subjects with HI titres ≥ 1:40 at Day 1 and Day 22 - FAS immunogenicity

Strain		aQIV (N = 1324)	Boostrix (N = 322)
	Day	HI ≥ 1:40 (% [95% CI])	
A/H1N1	N	1318	331
	Day 1	49.7% (46.96%, 52.43%)	50.5% (44.93%, 55.97%)
	N	1323	330
	Day 22	96.2% (95.05%, 97.18%)	46.7% (41.18%, 52.21%)
A/H3N2	N	1323	331
	Day 1	42.2% (39.50%, 44.89%)	39.6% (34.27%, 45.07%)
	N	1324	331
	Day 22	95.6% (94.37%, 96.66%)	41.7% (36.32%, 47.21%)
B/Yamagata	N	1315	330
	Day 1	24.1% (21.82%, 26.51%)	21.2% (16.93%, 26.02%)
	N	1320	330
	Day 22	79.2% (76.95%, 81.40%)	21.5% (17.20%, 26.35%)
B/Victoria	N	1314	331
	Day 1	21.2% (18.98%, 23.47%)	18.7% (14.67%, 23.36%)
	N	1320	331
	Day 22	81.6% (79.39%, 83.65%)	18.4% (14.40%, 23.03%)

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 percent of subjects with HI antibody titer ≥1:40 met or exceeded 60%.
Source: Table 14.2.1.2.

Percentages of Subjects Who Achieved Seroconversion

Table 31 summarises the proportion of subjects who achieved seroconversion post-vaccination at Day 22 in the FAS Immunogenicity.

Table 31: Number (%) of subjects with HI titre 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%.

Subgroup Analysis by Age, Comorbidity Score, Previous Vaccination Status, Sex, 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.

- **Summary of main efficacy results**

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

Table 32: Summary of efficacy for trial V118_18

Title: A Phase III, Randomised, Observer-Blind, Controlled, Multicentre 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 randomised, 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 randomised: 3381 subjects
	Boostrix		Combined Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed Number randomised: 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.
	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		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Full Analysis Set (FAS) Efficacy: Subjects in the All Enrolled Set who were randomised and received a study treatment, were under observation for at least 21 days post-vaccination and provided efficacy data.
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. <u>GMRs:</u> • 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). <u>Percentage of subjects with HI titre ⩾ 1:40</u>: • At Day 1, the percentage of subjects with HI titres ⩾ 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 titre ⩾ 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%).
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 randomised 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.

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%).

Study V118_23: A Phase 3, Randomised, Observer-blind, Controlled, Multicentre, Clinical Study to Evaluate Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine in Comparison with a Licensed Quadrivalent Influenza Vaccine, in Adults 50 to 64 Years of Age

Methods

- **Study Participants**

Inclusion criteria

Study participants were individuals 50 to 64 years of age (i.e. 50 to ≤64 years) on the day of the informed consent, who had voluntarily given written informed consent and could comply with study procedures including follow up.

Exclusion criteria

The main exclusion criteria were: Progressive, unstable or uncontrolled clinical conditions; Hypersensitivity to any component used in the study; history of any medical condition considered an AESI (e.g. Rheumatoid arthritis); Known history of Guillain Barré syndrome; Contraindication to intramuscular vaccination and blood draws and Abnormal function of the immune system due to clinical conditions, systemic administration of corticosteroids, or administration of antineoplastic and immunomodulating agents within 90 days prior to informed consent; Receipt of any influenza vaccine

within 6 months prior to enrolment, or plan to receive it during the study period.

It is noted that the applicant used a comorbidity risk score, which is a validated predictor of risk of complications from influenza in elderly subjects (65 years of age and older); a score of <50 is considered low risk and a score of ≥50 is considered high risk of complications from influenza. (Hak et al. 2004). As it is shown in the table here below, the comorbidity risk score assessment incorporates medical comorbidity and other baseline characteristics such as age, gender, outpatient visits during the previous year and previous hospitalisations due to pneumonia or influenza.

Table 33: Prediction rule for estimating the probability of hospitalisation due to pneumonia or influenza and death due to any cause (Hak et al. 2004)

Characteristic	Score[a]
Age, years	
<70	0
70-74	14
75-79	28
80-89	42
≥90	56
Sex	
Female	0
Male	9
Outpatient visits during the previous year	
0	0
1-6	11
7-12	22
>13	33
Previous hospitalization due to pneumonia or influenza	
No	0
Yes	63
Comorbidity[b]	
Pulmonary disease	18
Heart disease	6
Renal disease or renal transplant	12
Dementia or stroke	22
Non-hematological and hematological cancer	48
Subject total score	

Notes:

a. The prognostic score for a given subject can be obtained by adding the scores for each applicable characteristic.

b. Pre-existing medical conditions of eligible subjects will be scored following a judgment by the investigator.

- **Treatments**

There were two study vaccines in this study: the Investigational Vaccine aQIV (Fluad Tetra/Quadrivalent), and the Comparator Vaccine Fluarix Tetra/Quadrivalent (non-adjuvanted QIV) (GlaxoSmithKline Biologicals, Germany).

aQIV is an MF59-adjuvanted egg-derived subunit inactivated quadrivalent influenza virus vaccine manufactured by Seqirus.

Fluarix Tetra/Quadrivalent (nonadjuvanted QIV) is a nonadjuvanted egg-derived split inactivated quadrivalent influenza virus vaccine composed of antigens from 4 influenza strains: For both vaccines, the strain composition was that recommended by the World Health Organization (WHO) for quadrivalent influenza vaccines contemporaneous to the timing of the study, i.e., the Northern Hemisphere 2021/2022 influenza.

aQIV Vaccine (Fluad Tetra/Quadrivalent)	QIV Vaccine (Fluarix Tetra/Quadrivalent)
• A/Victoria/2570/2019 (IVR-215) (A/H1N1) (an A/Victoria/2570/2019 (H1N1)pdm09-like virus) • A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2) (an A/Cambodia/e0826360/2020 (H3N2)-like virus) • B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage) (a B/Phuket/3073/2013-like virus) • B/Victoria/705/2018 (BVR-11) (B/Victoria lineage) (a B/Washington/02/2019-like virus)	• A/Victoria/2570/2019 (IVR-215) (A/H1N1) (an A/Victoria/2570/2019 (H1N1)pdm09-like virus) • A/Tasmania/503/2020 (IVR-221) (A/H3N2) (an A/Cambodia/e0826360/2020 (H3N2)-like virus) • B/Phuket/3073/2013 (B/Yamagata lineage) (a B/Phuket/3073/2013-like virus) • B/Washington/02/2019 (B/Victoria lineage) (a B/Washington/02/2019-like virus)
Nominally 15 µg HA/strain	Nominally 15 µg HA/strain

- **Objectives**

Primary immunogenicity objectives:

1a. To demonstrate immunological noninferiority of aQIV versus a nonadjuvanted quadrivalent influenza comparator (QIV) in subjects 50-64 years of age, as measured by hemagglutination inhibition (HI) GMTs and SCRs for each vaccine strain, at 3 weeks after vaccination.

Success criteria: Noninferiority will be demonstrated if the upper limit (UL) of the 95% confidence interval (CI) for the inter-group GMT ratio1 (QIV/aQIV) is ≤1.5 for each vaccine strain, and the UL of the 95% CI for the difference in SCR2 (QIV – aQIV) is ≤10% for each vaccine strain.

1b. To demonstrate that aQIV induces a superior immune response compared with QIV in subjects 50-64 years of age as measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains.

Success criteria: Superior immune response will be demonstrated if the UL of the 95% CI for the inter-group GMT ratio (QIV/aQIV) is <1.0 for at least 2 of the 4 vaccine strains.

Secondary immunogenicity objectives:

2a. To demonstrate that aQIV induces a superior immune response compared with QIV in subjects 50-64 years of age as measured by HI GMT for at least one vaccine strain at 3 weeks after vaccination.

Success criteria: Superior immune response will be demonstrated if the UL of the 98.73% CI for the inter- group GMT ratio (QIV/aQIV) is <0.67 for one or more vaccine strains.

2b. To demonstrate greater persistence of the immune response for at least one vaccine strain at 6 months after vaccination with aQIV compared with QIV as measured by HI assay in subjects 50-64 years of age.

Success criteria: Greater persistence of the immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) is <1.0 for one or more vaccine strains.

2c. To evaluate the immunogenicity of aQIV compared with QIV as measured by HI in subjects 50-64 years of age.

Exploratory immunogenicity objectives

To evaluate persistence of the immune response at 9 months after vaccination with aQIV compared with QIV as measured by HI in subjects 50-64 years of age.

To further evaluate the immunogenicity of aQIV compared with QIV in subjects 50-64 years of age, with alternative assays, if sera permit.

- **Outcomes/endpoints**

Primary immunogenicity endpoints:

Humoral immune responses in terms of HI antibody response against homologous egg-derived vaccine strains (A/H1N1, A/H3N2, B/Yamagata, and B/Victoria):

- GMT of HI antibodies at Day 22
- SCR defined as the percentage of subjects with either a prevaccination HI titre <1:10 and a post-vaccination (Day 22) HI titre ≥1:40, or with either a prevaccination HI titre ≥1:10 and a ≥4-fold increase in post-vaccination HI titre

The derived variables are:

- GMT ratios (QIV/aQIV) at Day 22 for each strain
- The inter-group differences in the SCRs (QIV – aQIV) at Day 22 for each strain

To evaluate the primary immunogenicity objectives 1a and 1b, the following derived variables of GMT ratios and SCR differences were assessed at Day 22:

1a. Noninferiority of aQIV compared to QIV was assessed for the eight primary endpoints of HI GMT ratio and SCR difference for each virus strain included in the vaccines as follows:

- The GMT ratio (QIV/aQIV) for the A/H1N1 strain
- The GMT ratio (QIV/aQIV) for the A/H3N2 strain
- The GMT ratio (QIV/aQIV) for the B strain (Yamagata lineage)
- The GMT ratio (QIV/aQIV) for the B strain (Victoria lineage)
- The difference between the SCR (QIV – aQIV) for the A/H1N1 strain
- The difference between the SCR (QIV – aQIV) for the A/H3N2 strain
- The difference between the SCR (QIV – aQIV) for the B strain (Yamagata lineage)
- The difference between the SCR (QIV – aQIV) for the B strain (Victoria lineage)

1b. A superior immune response of aQIV compared to QIV was assessed for the endpoints of HI GMT for each virus strain included in the vaccines as follows:

- The GMT ratio (QIV/aQIV) for the A/H1N1 strain

- The GMT ratio (QIV/aQIV) for the A/H3N2 strain
- The GMT ratio (QIV/aQIV) for the B strain (Yamagata lineage)
- The GMT ratio (QIV/aQIV) for the B strain (Victoria lineage)

Secondary immunogenicity endpoints:

Humoral immune response in terms of HI antibody response against homologous egg-derived vaccine strains (A/H1N1, A/H3N2, B/Yamagata, and B/Victoria):

- GMT of HI antibodies at Day 22 and Day 181

To evaluate the secondary immunogenicity objectives 2a and 2b, the following derived variables of GMT ratios were assessed:

2a. Superior immune response of aQIV compared to QIV was assessed for HI GMT for the strains included in the vaccines as follows:

- The GMT ratio (QIV/aQIV) at Day 22.

2b. Greater persistence of the immune response of aQIV compared to QIV was assessed for HIGMT for the strains included in the vaccines as follows:

- The GMT ratio (QIV/aQIV) at Day 181.

2c. To evaluate the immunogenicity of aQIV compared with QIV as measured by HI in subjects 50-64 years of age as follows:

- GMT of HI antibodies on Day 1, Day 22, and Day 181
- Geometric mean fold increase (GMFI): The geometric mean of the fold increase of post-vaccination HI titre over the prevaccination HI titre (Day 22/Day 1, Day 181/Day 1)
- The percentage of subjects with a titre ≥1:40 at Day 1, Day 22, and Day 181
- SCR: The percentage of subjects with either a prevaccination HI titre <1:10 and a post-vaccination HI titre ≥1:40 or a prevaccination titre ≥1:10 and a ≥4-fold increase in post-vaccination titre on Day 22 and Day 181

Exploratory immunogenicity endpoints

Persistence of the immune response of aQIV compared to QIV at Day 271 will be assessed for HI GMT and GMT ratio for all strains included in the vaccines in a similar fashion as for secondary immunogenicity objective 2b and through the same descriptive immune response parameters as presented for secondary immunogenicity objective 2c.

For this analysis, Day 1 serum samples obtained for the primary and secondary study objectives (noninferiority and superiority assessments) will be retested. Day 1 data from the exploratory assessment of persistence at 9 months will not replace data obtained for the primary and secondary endpoint analyses.

Additional exploratory immunogenicity endpoints that may be assessed in the study include the measures of immunogenicity of aQIV and QIV as determined by the HI or microneutralisation (MN) assay against homologous or heterologous strains at Day 1, Day 22, Day 181, and Day 271 (depending on availability of adequate sera and on assay availability).

- **Sample size**

The sample size of 2018 subjects has been calculated to achieve a 90% power based on the primary

endpoints: non-inferiority of GMT and SCR differences of aQIV vs QIV for all strains and superiority of GMT of aQIV vs QIV for at least 2/4 vaccine strains with a one-sided alpha of 2.5%. The assumptions for both endpoints and for each strain are based on the results from a similar study comparing trivalent Influenza vaccines (V7P38). This calculation takes into account a dropout rate of 10%.

The assumptions and operating characteristics of the sample size estimation are well described. The operating characteristics meet regulatory requirements and the sample size calculations appear adequate.

Thus with 1:1 randomisation, assuming that B/Victoria and B/Yamagata were similar, 1,816 evaluable subjects would provide an overall power of 90% to demonstrate the primary objectives of noninferiority and superiority of aQIV vs QIV with one-sided alpha=0.025. Assuming a 10% drop out rate, the total sample size for the study needed was 2,018.

- **Randomisation and Blinding (masking)**

An Interactive Response Technology (IRT) system was used in the study. Subjects were enrolled and stratified equally into two age groups (50 to ≤59 years and 60 to ≤64 years) with approximately 50% of subjects per age group. Within each age group, subjects were randomised to aQIV or QIV according to a 1:1 ratio. Stratification for history of any influenza vaccination within the previous 3 influenza seasons (yes/no) was applied to all subjects.

The study was an observer-blind study. During the treatment period of the study, designated and trained unblinded nurse(s), physician(s), or other qualified healthcare professionals were responsible for preparing and administering the study vaccines to the subjects. They were instructed not to reveal the identity of the study vaccines to the subject or to the investigative site personnel (i.e., blinded investigator and study nurse) involved in the monitoring of conduct of the trial, except in an emergency if unblinding in IRT was not possible. Vaccine administration was shielded from the subject and blinded study personnel. The unblinded personnel were not involved in data collection or data review such as safety assessments and/or in collection of study data after the vaccinations. Study vaccines were assigned through an IRT system.

All personnel involved in the conduct of the study or in the analysis of the final study results, or who had contact with study centres, remained blinded.

All personnel involved in processing samples and performing laboratory assays remained blinded to the treatment codes until all Day 271 serum samples had been tested and the results had been transferred.

- **Statistical methods**

Handling of Dropouts, Missing Data

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the immunogenicity analysis will comprise a complete case analysis only, without introducing any bias. Additional sensitivity analysis will be considered if the percentage of subjects with missing data is more than 10%.

Analysis Sets

All Enrolled Set

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

All Exposed Set

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

Full Analysis *Set (FAS)* Immunogenicity

All subjects in the All Enrolled Set who were randomised, received study vaccination and provided immunogenicity data at any time point.

In case of vaccination error, subjects in the FAS sets were analysed "as randomised" (i.e., according to the vaccine the subject was designated to receive, which may be different from the vaccine the subject actually received).

The FAS Immunogenicity was used for the Day 22 immunogenicity superiority comparisons and all secondary immunogenicity objectives. The FAS Immunogenicity was also used for a sensitivity analysis for the noninferiority analyses based on the PPS Immunogenicity.

Per Protocol Set (PPS) Immunogenicity

All subjects in the FAS Immunogenicity who:

- Had both Day 1 and Day 22 immunogenicity assessment
- Correctly received the vaccine (i.e., received the vaccine to which the subjects were randomised and at the scheduled time points)
- Had no protocol deviations leading to exclusion as defined prior to unblinding/analysis
- Were not excluded due to other reasons defined prior to unblinding or analysis

The PPS Immunogenicity was used for the immunogenicity non-inferiority comparisons and for a sensitivity analysis for the superiority analyses based on the FAS Immunogenicity, where applicable.

Subgroup Analyses

Adjusted and unadjusted immunogenicity analyses of the GMTs and SCRs were performed by stratifying for the following subgroups:

- Age cohort (50 to ≤59 years and 60 to ≤64 years)
- Previous vaccination history (Yes and No)
- Sex (Male and Female)
- Race (Black or African American; White; Other10)
- Ethnicity (Hispanic or Latino and Not Hispanic or Latino)
- Comorbidity risk score11 (<50 and ≥50)

The adjusted immunogenicity analyses were conducted using the same model as the primary analysis; if a subgroup was included in the model, it was removed from the model for the corresponding subgroup analysis.

The different populations sets (including those using for primary analysis: Full Analysis Set (FAS) Immunogenicity and Per Protocol Set (PPS) Immunogenicity) are considered adequate.

The approach proposed by the applicant implies: 1) using the FAS immunogenicity for testing objective 1b, and for testing the sensitivity analyses regrading objective 1a; 2) using the PPS immunogenicity for objective 1a, and for the sensitive analysis regarding objective 1b. This approach is considered in

line with the guideline (Points to Consider on Switching between Superiority and Non-Inferiority (CPMP/EWP/482/99)) and thus was considered acceptable.

Sequential Testing and Multiplicity

Adjustment for multiple comparison and multiplicity is reflected in the CI of the success criteria, which kept the type I error under 5%. For secondary endpoint analyses, sequential testing and significance level adjustment will be applied to keep type I error under 5%.

For four out of four strain successes, with α=0.05 for each strain, the overall type I error is α4=0.00000625.

For two out of four strain successes, with α=0.05 for each strain, the overall type I error is

$0.05^4 + 4 \times 0.05^3 \times 0.95 + 6 \times 0.05^2 \times 0.95^2 = 0.014019$.

For 1 out of four strain successes, with α=0.05 for each strain, the overall type I error is

1-0.954=0.1855.

Thus, for objective 1b): two out of four strain success, there is no need to adjust for α=0.05 to keep the overall type I error under 0.05. But for objectives 2a) and 2b): 1 out of four strain success, α needs to be adjusted to 0.01274 so that the overall type I error =1-(1- 0.01274)4=0.0499944 which is less than 0.05. Therefore, the CI for the secondary objectives 2a and 2b have been adjusted to 98.73% to keep overall family wise error rate (FWER) under 0.05.

Confirmatory flow of tests and objectives, using a hierarchical testing approach

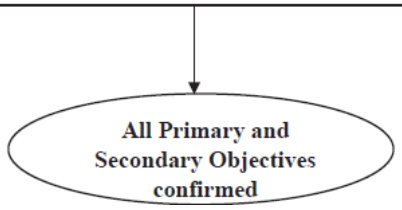
As soon as any success criterion is not met, confirmatory testing will stop.

PRIMARY OBJECTIVE 1a: Non-inferiority	
Tests using Antibody titer at Day 22: UL of 95% CI for GMT ratio (QIV/aQIV) for strain i ≤1.5 and UL of 95% CI for SCR difference (QIV-aQIV) for strain i ≤10%, for all i, i = 1 to 4	**Multiplicity consideration:** not required, overall type I error is < α, where α =0.05
	Analysis Set: PPS
Criterion: UL ≤ threshold for all 8 CIs => Non-inferiority confirmed and continue testing	

PRIMARY OBJECTIVE 1b: Superiority for at least 2 strains - basic threshold	
Tests using Antibody titer at Day 22: UL of 95% CI for GMT ratio (QIV/aQIV) for strain i <1.0, for at least 2 out of 4 strains	**Multiplicity consideration:** not required, overall type I error is < α
	Analysis Set: FAS
Criterion: CI UL < threshold for at least 2 out of 4 strains => Superiority (basic threshold) confirmed and continue testing	

SECONDARY OBJECTIVE 2a: Superiority for at least 1 strain - higher threshold	
Tests using Antibody titer at Day 22: UL of 98.73% CI for GMT ratio (QIV/aQIV) for strain i <0.67, for at least 1 out of 4 strains	**Multiplicity consideration:** α-adjusted CI
	Analysis Set: FAS
Criterion: CI UL < threshold for at least 1 strain => Superiority (higher threshold) confirmed and continue testing	

SECONDARY OBJECTIVE 2b: Persistence for at least 1 strain - Day 181	
Tests using Antibody titer at Day 181: UL of 98.73% CI for GMT ratio (QIV/aQIV) for strain i <1.0, for at least 1 out of 4 strains	**Multiplicity consideration:** α-adjusted CI
	Analysis Set: FAS
Criterion: CI UL < threshold for at least 1 strain => Persistence at Day 181 confirmed and continue testing	



Statistical Hypothesis

Noninferiority of aQIV to QIV (Objective 1a)

The statistical hypotheses to be tested for the primary immunogenicity objective 1a correspond to:

H0: *GMTri* >1.5, for any strain

Ha: *GMTri* ≤1.5, for all strains

and

H0: *Di* >10%, for any strain

Ha: *Di* ≤10%, for all strains

where *GMTri* (*i*=1,2,3,4) is any of the 4 strain-specific Day 22 GMT ratios, namely,

- *GMTr1*=GMTQIV/GMTaQIV for A/H1N1 strain
- *GMTr2*=GMTQIV/GMTaQIV for A/H3N2 strain
- *GMTr3*=GMTQIV/GMTaQIV for B/Yamagata strain

- *GMTr4*=GMTQIV/GMTaQIV for B/Victoria strain

and *Di* (*i*=1,2,3,4) is the 4 strain-specific Day 22 SCR differences (**π**QIV,i – **π**aQIV,i), namely,

- D1=**π**QIV,1 – **π**aQIV,1 for A/H1N1 strain
- D2=**π**QIV,2 – **π**aQIV,2 for A/H3N2 strain
- D3= **π**QIV,3 – **π**aQIV,3 for B/Yamagata strain
- D4= **π**QIV,4 – **π**aQIV,4 for B/Victoria strain

where **π**QIV,i, **π**aQIV,i (*i*=1,2,3,4) denotes the SCRs for the 4 strains in QIV and aQIV respectively.

Superiority of aQIV to QIV (Objective 1b)

The statistical hypotheses to be tested for the primary immunogenicity objective 1b correspond

to:

H0: GMTri ≥1, for at least 3 of the 4 vaccine strains at Day 22

Ha: GMTri <1, for at least 2 of the 4 vaccine strains at Day 22

where *GMTri* (*i*=1,2,3,4) are defined as above.

Superiority of aQIV vs QIV (higher threshold) (Objective 2a)

The statistical hypotheses to be tested for the secondary immunogenicity 2a correspond to:

H0: GMTr ≥0.67, for all four vaccine strains at Day 22

Ha: GMTr <0.67, for one or more vaccine strains at Day 22

where GMTr is the Day 22 GMT ratios of GMTQIV/GMTaQIV for that vaccine strain.

Persistence of immune response of aQIV compared to QIV (Objective 2b)

To demonstrate greater persistence of the immune response for at least one of the vaccine strains at 6 months after vaccination with aQIV compared with QIV as measured by HI assay in subjects 50-64 years of age, the statistical hypotheses to be tested for the secondary immunogenicity 2b correspond to:

H0: GMTr ≥1, for all four vaccine strains at Day 181

Ha: GMTr <1, for one or more vaccine strains at Day 181

where GMTr is 6-month GMT ratio of GMTQIV/GMTaQIV for that strain.

Immunogenicity of aQIV compared with QIV (Objective 2c)

There was no statistical hypothesis for secondary immunogenicity objective 2c.

Results

- **Participant flow**

The study population (N=2044) was slightly larger than the planned sample size of 2018 subjects because subjects who were already scheduled for enrolment, at the time the Sponsor was notified that the enrolment target had been reached, were allowed to participate in the study.

A total of 2044 subjects 50 to 64 years of age were enrolled in the study (All Enrolled Set) and randomised in a 1:1 ratio to receive aQIV or QIV. One subject was randomised to the QIV group but did not receive study vaccine and thus the All Exposed Set included 2043 subjects.

The majority of subjects (1971/2044 subjects, 96.4%) completed the study (Table 34:). The most common reason for discontinuing from the study was lost to follow-up (52/2044 subjects, 2.5%).

Table 34: Study disposition (all enrolled set)

	aQIV N=1027 n (%)	QIV N=1017 n (%)	Total N=2044 n (%)
Number of subjects enrolled	1027	1017	2044
Number of subjects randomized	1027 (100.0)	1017 (100.0)	2044 (100.0)
Number of subjects exposed	1027 (100.0)	1016 (99.9)	2043 (99.9)
Number of subjects completed study	982 (95.6)	989 (97.2)	1971 (96.4)
Discontinuation from the study	**45 (4.4)**	**28 (2.8)**	**73 (3.6)**
Primary reason for discontinuation			
Adverse Event	0	1 (0.1)	1 (0.0)
Death	1 (0.1)	0	1 (0.0)
Lost to Follow-up	35 (3.4)	17 (1.7)	52 (2.5)
Protocol Deviation	0	0	0
Related to COVID-19	0	0	0
Study Termination by Sponsor	0	0	0
Withdrawal of Consent	6 (0.6)	8 (0.8)	14 (0.7)
Other	3 (0.3)	2 (0.2)	5 (0.2)

Source: Table 14.1.2.
Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; QIV = Quadrivalent Influenza Vaccine.
Note 1: The percentages are based on the number of randomized subjects in each group.

The disposition flowchart is provided in Figure 4.

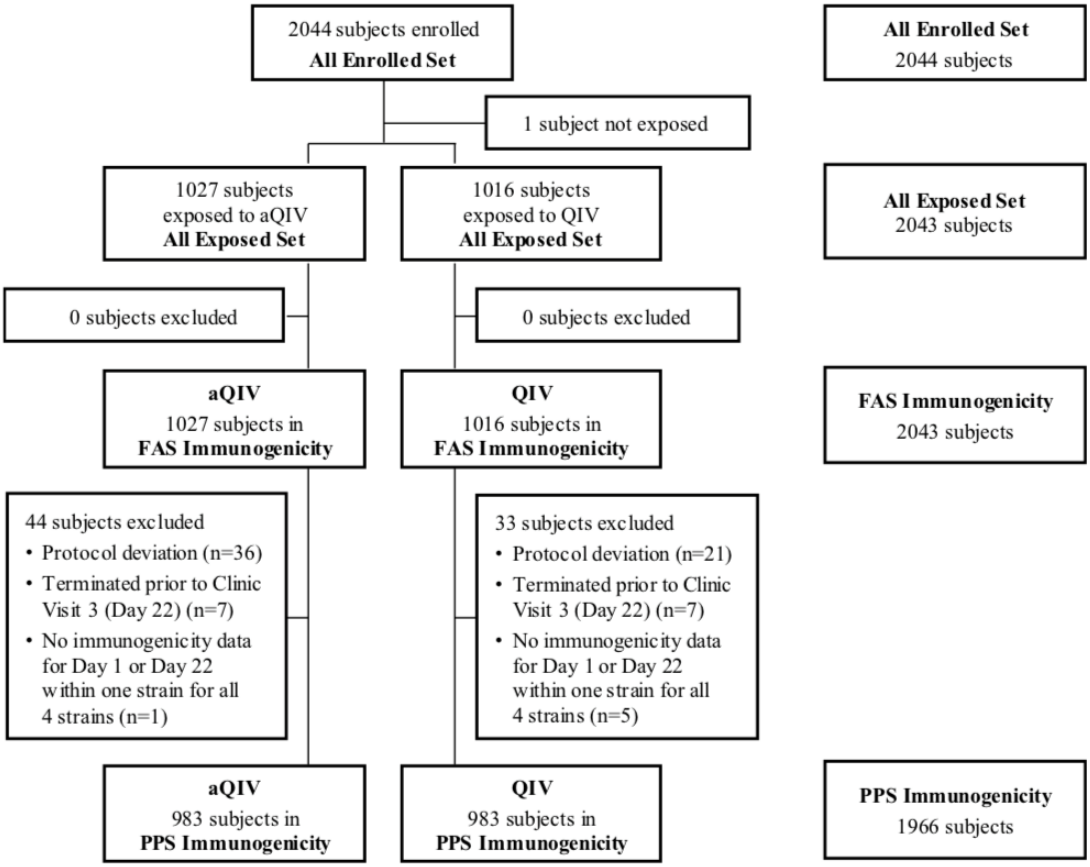


Figure 4: participant flow

- **Recruitment**

The study was conducted in Estonia (787 subjects), Germany (513 subjects), and the US (744 subjects). All subjects were recruited on the Northern Hemisphere 2021/2022 influenza season.

- **Conduct of the study**

Protocol amendments

Two protocol amendments were made during the study. The protocol amendments were implemented after First Subject First Visit and before Last Subject Last Visit (i.e., while the study was still blinded).

The main changes for the first protocol amendment (Version 1.0 (15 Apr 2021) to Version 2.0 (18 Nov 2021)) were:

1. Updating of the CI for secondary objectives 2a and 2b to reflect the correct alpha (correcting 95% for 98.73%).
2. Conducting database lock and unblinding in two stages to allow expedited CSR reporting. A Blinding Maintenance Plan was prepared to ensure blinding of relevant laboratory and statistical personnel was maintained until their activities had been completed.
3. Clarification of Exclusion Criteria #7b and #9, based on Estonian regulatory agency feedback.

4. Clarifications of reporting requirements for solicited AEs that start during Day 1-7 and continue beyond Day 14.
5. Correction of how the FAS would be analysed in case of vaccination errors, based on FDA regulatory agency feedback (subjects analysed "as randomised", as opposed to the previous "as treated").

The main changes for the second protocol amendment (Version 2.0 (18 Nov 2021) to Version 3.0 (11 Jul 2022)) were:

1. Reclassification of the secondary objective of immunogenicity persistence at 9 months after vaccination (Day 271) as an exploratory objective in order to expedite the primary and secondary immunogenicity results and report them with the complete safety data to support timely license applications in different regions.
2. Improvement in the definition of previous influenza vaccination as a stratification factor to consider subjects who had received an influenza vaccination in the previous 3 influenza seasons as previously vaccinated subjects (Yes) in order to acknowledge variability in timing of the annual influenza vaccination campaigns.
3. Correction of an inconsistency in the assessment and reporting of local solicited reactions to consider local events as being present if they measured ≥25 mm to ensure consistency with the approved labelling information for aQIV (Fluad Quadrivalent/Quad/Tetra).

In relation to the planned analysis, in the first analysis made by the applicant, the HI data used for the primary and secondary immunogenicity analyses excluded a number of samples (named "NRR-inconsistent" by the testing laboratory –) from these analyses. These samples corresponded to 45 subjects across the 4 vaccine strains (A/H1N1: 25 subjects; A/H3N2: 11 subjects; B/Yamagata: 6 subjects; B/Victoria: 10 subjects). Although according to the SOP, these samples could have been retested, the applicant decided not to include these samples in the initial analyses for the primary objectives since they had enough number of samples considering that the target enrolment levels had been exceeded and the dropout rate was smaller than anticipated.

After database lock and the initial statistical analysis of the primary study objectives (that resulted in not meeting the superiority primary endpoint, as described below), the applicant decided to retest (in a blinded manner) the "NRR-inconsistent" serum samples. The primary and secondary analyses were then recalculated taking into account these new additional samples (analysis on the complete serology dataset).

The applicant conducted a post-hoc sensitivity analysis based on the "Complete Serology Dataset". The applicant indicated that the additional samples included in the complete serology dataset corresponded to 45 subjects across the 4 vaccine strains (A/H1N1: 25 subjects; A/H3N2: 11 subjects; B/Yamagata: 6 subjects; B/Victoria: 10 subjects).

- **Baseline data**

The mean age of the All Enrolled Set was 57.8 years (SD: 4.19), with a range of 50 to 64 years, consistent with the intended study population. It is noted that more subjects (59%) were enrolled in the 50 to 59 years age cohort than in the 60 to 64 years age cohort (41%). Similarly, there more females (61%) than males (39%) enrolled in the trial.

There were no notable differences in the distribution of demographic and baseline characteristics between the aQIV and QIV vaccine groups, as shown in the following table.

Table 35: Demographics and baseline characteristics in subjects 50 to 64 years of age (all enrolled set)

	aQIV N=1027	QIV N=1017	Total N=2044
Age (years)			
n	1027	1017	2044
Mean (SD)	57.8 (4.17)	57.8 (4.21)	57.8 (4.19)
Min, max	50, 64	50, 64	50, 64
Age group (n [%])			
n	1027	1017	2044
50 to 59 years	609 (59.3)	596 (58.6)	1205 (59.0)
60 to 64 years	418 (40.7)	421 (41.4)	839 (41.0)
Sex (n [%])			
n	1027	1017	2044
Male	392 (38.2)	402 (39.5)	794 (38.8)
Female	635 (61.8)	615 (60.5)	1250 (61.2)
Race (n [%])			
n	1027	1017	2044
American Indian or Alaska Native	2 (0.2)	3 (0.3)	5 (0.2)
Asian	2 (0.2)	4 (0.4)	6 (0.3)
Black or African American	39 (3.8)	36 (3.5)	75 (3.7)
Native Hawaiian or Other Pacific Islander	1 (0.1)	1 (0.1)	2 (0.1)
White	982 (95.6)	972 (95.6)	1954 (95.6)
Other	1 (0.1)	1 (0.1)	2 (0.1)
Ethnic origin (n [%])			
n	1027	1017	2044
Hispanic or Latino	14 (1.4)	12 (1.2)	26 (1.3)
Not Hispanic or Latino	1013 (98.6)	1001 (98.4)	2014 (98.5)
Not reported	0	3 (0.3)	3 (0.1)
Unknown	0	1 (0.1)	1 (0.0)
Received an influenza vaccination in the previous 3 influenza seasons (n [%])			
n	1027	1017	2044
Yes	586 (57.1)	598 (58.8)	1184 (57.9)
No	441 (42.9)	419 (41.2)	860 (42.1)

	aQIV N=1027	QIV N=1017	Total N=2044
Comorbidity risk score (n [%])			
n	1027	1017	2044
<50	912 (88.8)	919 (90.4)	1831 (89.6)
≥50	115 (11.2)	98 (9.6)	213 (10.4)
Body mass index (kg/m²)			
n	1026	1016	2042
Mean (SD)	30.13 (6.553)	30.30 (6.760)	30.22 (6.656)
Median	29.13	29.19	29.17
Min, max	16.3, 71.2	16.6, 60.7	16.3, 71.2
Country (n [%])			
n	1027	1017	2044
Estonia	391 (38.1)	396 (38.9)	787 (38.5)
Germany	259 (25.2)	254 (25.0)	513 (25.1)
United States	377 (36.7)	367 (36.1)	744 (36.4)

Source: Table 14.1.3.1.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; QIV = Quadrivalent Influenza Vaccine; SD = standard deviation.

Note 1: The All Enrolled Set is displayed according to the randomized treatment.

Note 2: A comorbidity risk score of <50 is considered low probability of hospitalization due to pneumonia or influenza or death; a comorbidity risk score of ≥50 is considered high probability of hospitalization due to pneumonia or influenza or death (Hak et al. 2004).

- **Numbers analysed**

The numbers of subjects included in the immunogenicity analysis sets are shown in Table 36. All subjects in the All Exposed Set were included in the FAS Immunogenicity (N=2043) while 77 subjects

were excluded from the PPS Immunogenicity (N=1966), most commonly for protocol deviations (57 subjects) (Table 37).

Table 36: Overview of immunogenicity sets analysed (all enrolled set)

	aQIV N=1027 n (%)	QIV N=1017 n (%)	Total N=2044 n (%)
All Enrolled Set	1027 (100.0)	1017 (100.0)	2044 (100.0)
All Exposed Set	1027 (100.0)	1016 (99.9)	2043 (99.9)
FAS Immunogenicity	1027 (100.0)	1016 (99.9)	2043 (99.9)
PPS Immunogenicity	983 (95.7)	983 (96.7)	1966 (96.2)

Source: Table 14.1.1.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; FAS = Full Analysis Set; PPS = Per Protocol Set; QIV = Quadrivalent Influenza Vaccine.

Note 1: The All Enrolled Set and FAS Immunogenicity are displayed according to the randomized treatment. The All Exposed Set and PPS Immunogenicity are displayed according to the actual treatment.

The FAS Immunogenicity that was based on the complete serology dataset was identical to the FAS Immunogenicity for the first analysis in terms of the number of subjects, but included additional data points for individual vaccine strains.

The PPS Immunogenicity that was based on the complete serology dataset, included 2 more subjects in the QIV group compared with the PPS Immunogenicity for the first analysis. The PPS Immunogenicity for the complete serology dataset therefore consisted of 983 subjects in the aQIV group and 985 subjects in the QIV group for a total of 1968 subjects.

Table 37: Number of subjects and reason of exclusion from immunogenicity sets (FAS immunogenicity and PPS immunogenicity)

	aQIV N=1027 n (%)	QIV N=1017 n (%)	Total N=2044 n (%)
All Enrolled Set	**1027 (100.0)**	**1017 (100.0)**	**2044 (100.0)**
Randomized but not treated	0	1 (0.1)	1 (0.0)
All Exposed Set	**1027 (100.0)**	**1016 (99.9)**	**2043 (99.9)**
Randomized and treated but no immunogenicity data available	0	0	0
FAS Immunogenicity	**1027 (100.0)**	**1016 (99.9)**	**2043 (99.9)**
Terminated prior to Clinic Visit 3 (Day 22)	7 (0.7)	7 (0.7)	14 (0.7)
No immunogenicity data for primary immunogenicity samples	1 (0.1)	5 (0.5)	6 (0.3)
Protocol deviation	36 (3.5)	21 (2.1)	57 (2.8)
Serum sample collected outside time window specified in the protocol	19 (1.9)	12 (1.2)	31 (1.5)
Subject does not meet at least 1 inclusion or exclusion criterion	16 (1.6)	8 (0.8)	24 (1.2)
Subject received a kit number other than the one assigned at randomization	1 (0.1)	1 (0.1)	2 (0.1)
PPS Immunogenicity	**983 (95.7)**	**983 (96.7)**	**1966 (96.2)**

Source: Table 14.1.1 and Table 14.1.7.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; FAS = Full Analysis Set; PPS = Per Protocol Set; QIV = Quadrivalent Influenza Vaccine.

Note 1: The All Enrolled Set and FAS Immunogenicity are displayed according to the randomized treatment. The All Exposed Set and PPS Immunogenicity are displayed according to the actual treatment.

Note 2: A subject was excluded from the PPS Immunogenicity for the reason of "No immunogenicity data for the primary immunogenicity samples" if results for at least one of the pivotal samples (Day 1, Day 22) were missing for all 4 vaccine strains.

Note 3: A subject was excluded from the PPS Immunogenicity for the reason of "Serum sample collected outside the time window specified in the protocol" if the Day 1 and/or Day 22 blood sample were taken out of window.

Note 4: Subject 27601-005 was randomized to the QIV group but withdrew before study vaccine administration. Subject 27604-022 was randomized to the QIV group but was vaccinated with aQIV. Subject 27604-023 was randomized to the aQIV group but was vaccinated with QIV.

- **Outcomes and estimation**

Primary endpoints

Non-inferiority Analysis of aQIV Versus QIV – Geometric Mean Titre Ratios (Study Objective 1a)

In the PPS Immunogenicity first analysis, the UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio did not exceed 1.5 for any of the 4 vaccine strains (A/H1N1: 0.87; A/H3N2: 0.99; B/Yamagata: 1.01; B/Victoria: 1.07) (Table 38). Therefore, the prespecified success criteria for demonstrating immunological noninferiority of aQIV versus a nonadjuvanted QIV were met with respect to the GMT ratio for all 4 vaccine strains in subjects 50 to 64 years of age.

Table 38: Post-vaccination GMT, GMT ratio, and analysis of noninferiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at Day 22 by HI assay (PPS immunogenicity)

	Adjusted Analysis			
	Day 22 GMT		GMT Ratio	
	aQIV N=983 (95% CI)	QIV N=983 (95% CI)	QIV over aQIV (95% CI)	Met predefined noninferiority criteria?
A/H1N1	735.20 (692.28, 780.78)	587.24 (552.90, 623.70)	0.80 (0.74, **0.87**)	Yes
A/H3N2	347.75 (324.63, 372.53)	314.38 (293.54, 336.70)	0.90 (0.82, **0.99**)	Yes
B/Yamagata	154.40 (146.79, 162.41)	145.72 (138.56, 153.26)	0.94 (0.88, **1.01**)	Yes
B/Victoria	144.35 (136.89, 152.21)	143.59 (136.21, 151.37)	0.99 (0.92, **1.07**)	Yes

Source: Table 14.2.1.1.1.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; GMT = geometric mean titer; HI = hemagglutination inhibition; PPS = Per Protocol Set; QIV = Quadrivalent Influenza Vaccine; UL = upper limit.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Adjusted analysis GMT model: $\log_{10}$ transformed postvaccination (Day 22) HI titer = vaccine group + age cohort + sex + influenza vaccination history + prevaccination titer ($\log_{10}$ transformed), with subsequent back-transformation.

Note 3: Noninferiority criteria for the GMT ratio: UL of the 95% CI for the inter-group GMT ratio (shown in bold text) is ≤1.5 for each vaccine strain.

Analysis on the Complete Serology Dataset: Noninferiority Analysis in the PPS Immunogenicity

For the complete serology dataset, the UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio did not exceed 1.5 for any of the 4 vaccine strains (A/H1N1: 0.87; A/H3N2: 0.99; B/Yamagata: 1.01; B/Victoria: 1.07) (Table 39) and, thus, the prespecified non-inferiority success criteria for the GMT ratio were met for all 4 vaccine strains in the PPS Immunogenicity. These results are consistent with the first analysis results based on the PPS Immunogenicity.

Table 39: Complete serology dataset: Post-vaccination GMT, GMT ratio, and analysis of noninferiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at day 22 by HI assay (PPS immunogenicity)

	Adjusted Analysis			
	Day 22 GMT		GMT Ratio	
	aQIV N=983 (95% CI)	QIV N=985 (95% CI)	QIV over aQIV (95% CI)	Met predefined noninferiority criteria?
A/H1N1	731.90 (689.39, 777.04)	586.85 (552.83, 622.96)	0.80 (0.74, **0.87**)	Yes
A/H3N2	347.89 (324.78, 372.64)	313.16 (292.42, 335.36)	0.90 (0.82, **0.99**)	Yes
B/Yamagata	154.40 (146.80, 162.40)	145.74 (138.57, 153.27)	0.94 (0.88, **1.01**)	Yes
B/Victoria	144.41 (136.97, 152.26)	143.32 (135.97, 151.07)	0.99 (0.92, **1.07**)	Yes

Source: Table 14.2.1.1.1.s.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; GMT = geometric mean titer; HI = hemagglutination inhibition; PPS = Per Protocol Set; QIV = Quadrivalent Influenza Vaccine; UL = upper limit.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Adjusted analysis GMT model: log10 transformed postvaccination (Day 22) HI titer = vaccine group + age cohort + sex + influenza vaccination history + prevaccination titer (log10 transformed), with subsequent back-transformation.

Note 3: Noninferiority criteria for the GMT ratio: UL of the 95% CI for the inter-group GMT ratio (shown in bold text) is ≤1.5 for each vaccine strain.

Sensitivity Analysis: Non-inferiority Analysis in the FAS Immunogenicity

The UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio did not exceed 1.5 for any of the 4 vaccine strains (A/H1N1: 0.87; A/H3N2: 1.002; B/Yamagata: 1.01; B/Victoria: 1.08) and, thus, the prespecified non-inferiority success criteria for the GMT ratio were met for all 4 vaccine strains in the FAS Immunogenicity. These results are consistent with the first analysis results based on the PPS Immunogenicity.

Sensitivity Analysis on the Complete Serology Dataset: Non-inferiority Analysis in the FAS Immunogenicity

The UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio did not exceed 1.5 for any of the 4 vaccine strains (A/H1N1: 0.88; A/H3N2: 0.998; B/Yamagata: 1.01; B/Victoria: 1.07) and, thus, the prespecified non-inferiority success criteria for the GMT ratio were met for all 4 vaccine strains in the complete serology dataset based on the FAS Immunogenicity. These results are consistent with the first and complete serology dataset analyses based on the PPS Immunogenicity.

Non-inferiority Analysis of aQIV Versus QIV – Seroconversion Rate Differences (Study Objective 1a)

In the PPS Immunogenicity first analysis, the UL of the 95% CI for the SCR difference did not exceed 10% for any of the 4 vaccine strains (A/H1N1: -0.89%; A/H3N2: 2.52%; B/Yamagata: 2.22%; B/Victoria: 0.87%) (Table 40). Therefore, the prespecified success criteria for demonstrating immunological non-inferiority of aQIV versus a non-adjuvanted QIV were met with respect to the SCR difference for all 4 vaccine strains in subjects 50 to 64 years of age.

Table 40: SCR, SCR difference, and analysis of noninferiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at day 22 by HI assay (PPS immunogenicity)

	Day 22 SCR		SCR Difference	
	aQIV N=983 % (95% CI)	QIV N=983 % (95% CI)	QIV minus aQIV % (95% CI)	Met predefined noninferiority criteria?
A/H1N1	81.0 (78.37, 83.43)	76.5 (73.64, 79.10)	-4.5 (-8.20, **-0.89**)	Yes
A/H3N2	63.4 (60.26, 66.46)	61.6 (58.44, 64.67)	-1.8 (-6.12, **2.52**)	Yes
B/Yamagata	43.2 (40.09, 46.43)	41.1 (37.96, 44.23)	-2.2 (-6.56, **2.22**)	Yes
B/Victoria	44.3 (41.10, 47.46)	40.7 (37.64, 43.89)	-3.5 (-7.91, **0.87**)	Yes

Source: Table 14.2.1.2.1.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; HI = hemagglutination inhibition; SCR = seroconversion rate; PPS = Per Protocol Set; QIV = Quadrivalent Influenza Vaccine; UL = upper limit.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Noninferiority criteria for the SCR difference: UL of the 95% CI for the difference in SCR (shown in bold text) is ≤10% for each vaccine strain.

Analysis on the Complete Serology Dataset: Non-inferiority Analysis in the PPS Immunogenicity

For the complete serology dataset, the UL of the 95% CI for the SCR difference did not exceed 10% for any of the 4 vaccine strains (A/H1N1: -0.74%; A/H3N2: 2.48%; B/Yamagata: 2.00%; B/Victoria: 0.45%) (Table 41) and, thus, the prespecified non-inferiority success criteria for the SCR difference were met for all 4 vaccine strains in the PPS Immunogenicity. These results are consistent with the first analysis results based on the PPS Immunogenicity.

Table 41: Complete serology dataset: SCR, SCR difference, and analysis of noninferiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at day 22 by HI assay (PPS immunogenicity)

	Day 22 SCR		SCR Difference	
	aQIV N=983 % (95% CI)	QIV N=985 % (95% CI)	QIV minus aQIV % (95% CI)	Met predefined noninferiority criteria?
A/H1N1	81.2 (78.57, 83.58)	76.8 (74.04, 79.42)	-4.4 (-7.97, **-0.74**)	Yes
A/H3N2	63.6 (60.46, 66.63)	61.8 (58.61, 64.82)	-1.8 (-6.14, **2.48**)	Yes
B/Yamagata	43.4 (40.27, 46.60)	41.0 (37.92, 44.19)	-2.4 (-6.77, **2.00**)	Yes
B/Victoria	44.5 (41.39, 47.74)	40.6 (37.52, 43.76)	-3.9 (-8.31, **0.45**)	Yes

Source: Table 14.2.1.2.1.s.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; HI = hemagglutination inhibition; SCR = seroconversion rate; PPS = Per Protocol Set; QIV = Quadrivalent Influenza Vaccine; UL = upper limit.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Noninferiority criteria for the SCR difference: UL of the 95% CI for the difference in SCR (shown in bold text) is ≤10% for each vaccine strain.

Sensitivity Analysis: Non-inferiority Analysis in the FAS Immunogenicity

The UL of the 95% CI for the SCR difference did not exceed 10% for any of the 4 vaccine strains (A/H1N1: -0.31%; A/H3N2: 2.62%; B/Yamagata: 2.70%; B/Victoria: 1.34%) and, thus, the prespecified non-inferiority success criteria for the SCR difference were met for strains in the FAS Immunogenicity. These results are consistent with the first analysis results based on the PPS Immunogenicity.

Sensitivity Analysis on the Complete Serology Dataset: Non-inferiority Analysis in the FAS Immunogenicity

The UL of the 95% CI for the SCR difference did not exceed 10% for any of the 4 vaccine strains (A/H1N1: -0.17%; A/H3N2: 2.58%; B/Yamagata: 2.49%; B/Victoria: 0.93%) and, thus, the prespecified non-inferiority success criteria for the SCR difference were met for all 4 vaccine strains in the complete serology dataset based on the FAS Immunogenicity. These results are consistent with the first and complete serology dataset analyses based on the PPS Immunogenicity.

Non-inferiority Analysis of aQIV Versus QIV (Study Objective 1a)

All 8 primary non-inferiority endpoints (Study Objective 1a) were met in the PPS Immunogenicity first analysis:

- The UL of the 95% CI for the GMT ratio (QIV/aQIV) was below the non-inferiority margin of 1.5 for all 4 vaccine strains (A/H1N1: 0.87; A/H3N2: 0.99; B/Yamagata: 1.01; B/Victoria: 1.07).
- The UL of the 95% CI for the SCR difference (QIV – aQIV) was below the non-inferiority margin of 10% for all 4 vaccine strains (A/H1N1: -0.89%; A/H3N2: 2.52%; B/Yamagata: 2.22%; B/Victoria: 0.87%).

Similarly, the 8 primary non-inferiority endpoints (Study Objective 1a) were met in the PPS immunogenicity when using the complete serology dataset.

A sensitivity analyses performed in the FAS immunogenicity (both the initial analysis and that performed on the complete serology dataset) yielded again the same results (i.e., all 8 primary non-inferiority endpoints were met).

In conclusion, the pre-specified success criteria for Study Objective 1a were met, and thus the non-inferiority of aQIV compared with QIV in subjects 50 to 64 years of age was concluded.

Superiority Analysis of aQIV Versus QIV – Geometric Mean Titre Ratios (Study Objective 1b)

In the FAS Immunogenicity first analysis (Table 42), the UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio was:

- Below the superiority margin of 1.0 for the A/H1N1 strain (0.87)
- Above the superiority margin of 1.0 for the B/Yamagata (1.01) and B/Victoria (1.08) strains; the superiority margin was marginally exceeded for the A/H3N2 strain (1.002)

As the UL of the 95% CI in the first analysis was below the superiority margin of 1.0 for only 1 of the 4 vaccine strains (A/H1N1), the prespecified success criterion for demonstrating a superior immune response for aQIV compared with QIV was not met in subjects 50 to 64 years of age.

Table 42: Post-vaccination GMT, GMT ratio, and analysis of superiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at day 22 by HI assay (FAS immunogenicity)

	Adjusted Analysis			
	Day 22 GMT		GMT Ratio	
	aQIV N=1027 (95% CI)	QIV N=1016 (95% CI)	QIV over aQIV (95% CI)	Met predefined superiority criteria?
A/H1N1	732.37 (690.33, 776.98)	589.44 (555.31, 625.66)	0.80 (0.74, **0.87**)	Yes
A/H3N2	346.98 (324.30, 371.24)	316.91 (296.15, 339.12)	0.91 (0.83, **1.002**)	No
B/Yamagata	155.19 (147.66, 163.10)	146.88 (139.73, 154.39)	0.95 (0.88, **1.01**)	No
B/Victoria	143.66 (136.35, 151.37)	144.00 (136.65, 151.74)	1.00 (0.93, **1.08**)	No

Source: Table 14.2.1.1.2.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; FAS = Full Analysis Set; GMT = geometric mean titer; HI = hemagglutination inhibition; QIV = Quadrivalent Influenza Vaccine; UL = upper limit.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Adjusted analysis GMT model: $\log_{10}$ transformed postvaccination (Day 22) HI titer = vaccine group + age cohort + sex + influenza vaccination history + prevaccination titer ($\log_{10}$ transformed), with subsequent back-transformation.

Note 3: Superiority criteria for the GMT ratio: UL of the 95% CI for the inter-group GMT ratio (shown in bold text) is <1.0 for at least 2 of the 4 vaccine strains.

Note 4: Upper limit of 95% CI shows 3 decimal places to assess whether the interval excludes 1.0.

Analysis on the Complete Serology Dataset: Superiority Analysis in the FAS Immunogenicity

For the complete serology dataset, the point estimates of the Day 22 GMT ratios in the FAS Immunogenicity (Table 43) were consistent with those in the FAS Immunogenicity first analysis. In addition, the UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio in the FAS Immunogenicity was:

- Below the protocol-specified superiority margin of 1.0 for the A/H1N1 (0.88) and A/H3N2 (0.998) strains.
- Above the protocol-specified superiority margin of 1.0 for the B/Yamagata (1.01) and B/Victoria (1.07) strains.

Thus, for the complete serology dataset in the FAS Immunogenicity, a superior immune response was observed for aQIV compared with QIV for 2 of the 4 vaccine strains.

Table 43: Complete serology dataset: Post-vaccination GMT, GMT ratio, and analysis of superiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at day 22 by HI assay (FAS immunogenicity)

	Adjusted Analysis			
	Day 22 GMT		GMT Ratio	
	aQIV N=1027 (95% CI)	QIV N=1016 (95% CI)	QIV over aQIV (95% CI)	Met predefined superiority criteria?
A/H1N1	729.17 (687.51, 773.36)	589.07 (555.25, 624.94)	0.81 (0.74, **0.88**)	Yes
A/H3N2	347.09 (324.44, 371.33)	315.69 (295.04, 337.79)	0.91 (0.83, **0.998**)	Yes
B/Yamagata	155.19 (147.67, 163.09)	146.89 (139.74, 154.40)	0.95 (0.88, **1.01**)	No
B/Victoria	143.73 (136.44, 151.42)	143.74 (136.42, 151.45)	1.00 (0.93, **1.07**)	No

Source: Table 14.2.1.1.2.s.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; FAS = Full Analysis Set; GMT = geometric mean titer; HI = hemagglutination inhibition; QIV = Quadrivalent Influenza Vaccine; UL = upper limit.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Adjusted analysis GMT model: $\log_{10}$ transformed postvaccination (Day 22) HI titer = vaccine group + age cohort + sex + influenza vaccination history + prevaccination titer ($\log_{10}$ transformed), with subsequent back-transformation.

Note 3: Superiority criteria for the GMT ratio: UL of the 95% CI for the inter-group GMT ratio (shown in bold text) is <1.0 for at least 2 of the 4 vaccine strains.

Note 4: Upper limit of 95% CI shows 3 decimal places to assess whether the interval excludes 1.0.

Sensitivity Analysis: Superiority Analysis in the PPS Immunogenicity

The point estimates of the Day 22 GMT ratios in the PPS Immunogenicity were consistent with those in the primary FAS Immunogenicity; moreover, the UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio was below the superiority margin of 1.0 for 2 of the 4 vaccine strains in the PPS Immunogenicity, i.e., the A/H1N1 (0.87) and A/H3N2 (0.99) strains, and above for the B/Yamagata (1.01) and B/Victoria (1.07) strains. Thus, the prespecified criterion for demonstrating a superior immune response for aQIV compared with QIV for at least 2 strains was met in the PPS Immunogenicity.

Sensitivity Analysis on the Complete Serology Dataset: Superiority Analysis in the PPS Immunogenicity

The UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio was below the superiority margin of 1.0 for 2 of 4 vaccine strains, i.e., the A/H1N1 (0.87) and A/H3N2 (0.99) strains, and above for the B/Yamagata (1.01) and B/Victoria (1.07) strains. Thus, for the complete serology dataset in the PPS Immunogenicity, a superior immune response was observed for aQIV compared with QIV for 2 of the 4 vaccine strains.

Superiority Analysis of aQIV Versus QIV (Study Objective 1b)

In relation to objective 1b, in the FAS Immunogenicity first analysis, the UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio was:

- Below the superiority margin of 1.0 for the A/H1N1 strain (0.87).
- Above the superiority margin of 1.0 for the B/Yamagata (1.01) and B/Victoria (1.08) strains; the superiority margin was marginally exceeded for the A/H3N2 strain (1.002).

As the UL of the 95% CI in the first analysis was below the superiority margin of 1.0 for only 1 of the 4 vaccine strains (A/H1N1), the prespecified success criterion for demonstrating a superior immune response for aQIV compared with QIV was not met in subjects 50 to 64 years of age.

When the analysis was performed in the FAS Immunogenicity (complete serology dataset), the UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio was below the protocol specified superiority margin of 1.0 for two of the four strains (A/H1N1 (0.88) and AH3N2 (0.998)). Thus in this analysis, a superior immune response was observed for aQIV vs QIV for 2 of the 4 vaccine strains.

The sensitivity analysis performed in the PPS for immunogenicity (both the first analysis and the one performed in the complete serology dataset) demonstrated superiority of aQIV compared to QIV for two (A/H1N1 and A/H3N2) of the four vaccine strains.

Secondary Immunogenicity Endpoints

Superiority Analysis of aQIV Versus QIV (Higher Threshold) – Geometric Mean Titre Ratios (Study Objective 2a)

The aim of Study Objective 2a was to assess a higher threshold for superiority than that assessed in Study Objective 1b (i.e., a superiority margin of 0.67 versus a superiority margin of 1.0). As described above, confirmatory testing stopped at Study Objective 1b and thus analysis of superiority of aQIV versus QIV at the higher superiority margin of 0.67 (Study Objective 2a) was not conducted; as a result, the secondary immunogenicity analysis for Study Objective 2a is provided below for descriptive purposes only.

Table 44: Post-vaccination GMP, GMT ratio, and analysis of higher threshold for superiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at day 22 by HI assay (FAS immunogenicity)

	Adjusted Analysis		
	Day 22 GMT		GMT Ratio
	aQIV N=1027 (95% CI)	QIV N=1016 (95% CI)	QIV over aQIV (95% CI)
A/H1N1	732.37 (690.33, 776.98)	589.44 (555.31, 625.66)	0.80 (0.74, 0.87)
A/H3N2	346.98 (324.30, 371.24)	316.91 (296.15, 339.12)	0.91 (0.83, 1.00)
B/Yamagata	155.19 (147.66, 163.10)	146.88 (139.73, 154.39)	0.95 (0.88, 1.01)
B/Victoria	143.66 (136.35, 151.37)	144.00 (136.65, 151.74)	1.00 (0.93, 1.08)

Source: Table 14.2.1.1.2.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; FAS = Full Analysis Set; GMT = geometric mean titer; HI = hemagglutination inhibition; QIV = Quadrivalent Influenza Vaccine.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Adjusted analysis GMT model: $\log_{10}$ transformed postvaccination (Day 22) HI titer = vaccine group + age cohort + sex + influenza vaccination history + prevaccination titer ($\log_{10}$ transformed), with subsequent back-transformation.

Persistence of the Immune Response of aQIV Compared to QIV (Study Objective 2b)

As described above, the secondary immunogenicity analysis of Day 181 HI GMTs for Study Objective 2b is provided for descriptive purposes only.

The Day 181 HI GMT was observed to be higher for the A/H1N1 strain in the aQIV group compared with the QIV group (Table 45). There were no notable differences in Day 181 HI GMTs between the two vaccine groups for the A/H3N2, B/Yamagata, and B/Victoria strains.

Table 45: Post-vaccination GMT, GMT ratio, and analysis of persistence of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at Day 181 by HI assay (FAS immunogenicity)

	Adjusted Analysis		
	Day 181 GMT		GMT Ratio
	aQIV N=1027 (95% CI)	QIV N=1016 (95% CI)	QIV over aQIV (95% CI)
A/H1N1	356.25 (335.81, 377.94)	308.52 (290.78, 327.33)	0.87 (0.80, 0.94)
A/H3N2	165.43 (156.09, 175.33)	157.79 (148.90, 167.21)	0.95 (0.88, 1.03)
B/Yamagata	83.62 (79.98, 87.42)	84.71 (81.03, 88.55)	1.01 (0.95, 1.08)
B/Victoria	79.83 (76.10, 83.75)	81.82 (78.00, 85.82)	1.02 (0.96, 1.09)

Source: Table 14.2.1.1.2.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; FAS = Full Analysis Set; GMT = geometric mean titer; HI = hemagglutination inhibition; QIV = Quadrivalent Influenza Vaccine.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Adjusted analysis GMT model: $\log_{10}$ transformed postvaccination (Day 181) HI titer = vaccine group + age cohort + sex + influenza vaccination history + prevaccination titer ($\log_{10}$ transformed), with subsequent back-transformation.

Immunogenicity of aQIV Compared with QIV (Study Objective 2c)

The unadjusted analyses of HI GMTs, GMFIs, percentage of subjects with HI titre ≥1:40, and SCRs are presented for the FAS Immunogenicity in Table 46 and summarised below. The results in the complete serology dataset are consistent with the results summarised below. No formal statistical comparisons were made between the aQIV and QIV groups.

Table 46: Pre - and post-vaccination GMT, GMFI, percentage of subjects with titre ≥1:40, and seroconversion rates in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria by HI assay (FAS immunogenicity)

Unadjusted Analysis	aQIV N=1027 No./% (95% CI)	QIV N=1016 No./% (95% CI)
A/H1N1		
Day 1 HI GMT	55.36 (50.61, 60.54)	51.83 (47.43, 56.64)
Day 22 HI GMT	709.25 (667.01, 754.16)	553.26 (518.35, 590.52)
Day 181 HI GMT	332.75 (310.23, 356.90)	277.23 (258.07, 297.82)
Fold increase Day 22 HI Titer	12.85 (11.72, 14.10)	10.68 (9.78, 11.66)
Fold increase Day 181 HI Titer	6.15 (5.65, 6.69)	5.34 (4.91, 5.81)
Day 1 % HI Titer ≥1:40	65.7 (62.68, 68.64)	65.0 (61.93, 67.96)
Day 22 % HI Titer ≥1:40	99.7 (99.13, 99.94)	99.2 (98.42, 99.65)
Day 181 % HI Titer ≥1:40	98.3 (97.23, 98.98)	96.2 (94.81, 97.32)
Day 22 SCR (%) HI Titer	80.6 (78.05, 83.05)	76.7 (73.96, 79.34)
Day 181 SCR (%) HI Titer	64.5 (61.38, 67.51)	55.5 (52.28, 58.64)
A/H3N2		
Day 1 HI GMT	46.29 (42.34, 50.61)	46.85 (42.92, 51.15)
Day 22 HI GMT	322.97 (300.31, 347.34)	293.31 (272.44, 315.78)
Day 181 HI GMT	152.10 (141.42, 163.58)	143.94 (133.46, 155.25)
Fold increase Day 22 HI Titer	7.04 (6.38, 7.76)	6.28 (5.75, 6.86)
Fold increase Day 181 HI Titer	3.27 (3.02, 3.54)	3.06 (2.85, 3.30)
Day 1 % HI Titer ≥1:40	60.5 (57.35, 63.51)	61.9 (58.79, 64.91)
Day 22 % HI Titer ≥1:40	97.5 (96.37, 98.39)	97.3 (96.11, 98.22)
Day 181 % HI Titer ≥1:40	92.0 (90.15, 93.64)	89.9 (87.88, 91.74)
Day 22 SCR (%) HI Titer	63.2 (60.16, 66.25)	61.6 (58.48, 64.65)
Day 181 SCR (%) HI Titer	39.3 (36.17, 42.44)	38.4 (35.35, 41.58)

Unadjusted Analysis	aQIV N=1027 No./% (95% CI)	QIV N=1016 No./% (95% CI)
B/Yamagata		
Day 1 HI GMT	38.74 (36.05, 41.63)	38.33 (35.68, 41.18)
Day 22 HI GMT	144.53 (136.22, 153.35)	133.94 (126.12, 142.26)
Day 181 HI GMT	77.08 (72.51, 81.93)	77.34 (72.72, 82.25)
Fold increase Day 22 HI Titer	3.75 (3.48, 4.04)	3.50 (3.25, 3.77)
Fold increase Day 181 HI Titer	2.02 (1.90, 2.15)	2.01 (1.89, 2.14)
Day 1 % HI Titer ≥1:40	61.0 (57.94, 64.05)	61.9 (58.81, 64.90)
Day 22 % HI Titer ≥1:40	95.9 (94.45, 97.00)	94.6 (93.04, 95.93)
Day 181 % HI Titer ≥1:40	84.0 (81.51, 86.21)	84.0 (81.60, 86.28)
Day 22 SCR (%) HI Titer	42.7 (39.64, 45.86)	41.1 (38.03, 44.24)
Day 181 SCR (%) HI Titer	22.3 (19.71, 25.05)	22.4 (19.86, 25.19)
B/Victoria		
Day 1 HI GMT	36.39 (33.92, 39.05)	37.09 (34.59, 39.77)
Day 22 HI GMT	134.43 (126.20, 143.20)	132.94 (124.77, 141.64)
Day 181 HI GMT	74.53 (70.00, 79.36)	76.17 (71.58, 81.05)
Fold increase Day 22 HI Titer	3.71 (3.44, 4.00)	3.61 (3.34, 3.89)
Fold increase Day 181 HI Titer	2.06 (1.93, 2.19)	2.06 (1.92, 2.20)
Day 1 % HI Titer ≥1:40	58.8 (55.71, 61.87)	60.5 (57.42, 63.55)
Day 22 % HI Titer ≥1:40	94.4 (92.76, 95.70)	93.3 (91.59, 94.79)
Day 181 % HI Titer ≥1:40	83.5 (81.00, 85.77)	84.3 (81.89, 86.54)
Day 22 SCR (%) HI Titer	43.7 (40.57, 46.80)	40.7 (37.61, 43.80)
Day 181 SCR (%) HI Titer	24.4 (21.68, 27.18)	23.6 (21.01, 26.44)

Source: Table 14.2.2.1.2 and Table 14.2.2.2.2.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; FAS = Full Analysis Set; GMT = geometric mean titer; GMFI = geometric mean fold increase; HI = hemagglutination inhibition; QIV = Quadrivalent Influenza Vaccine; SCR = seroconversion rate.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: GMT and GMFI with corresponding CIs were calculated on $\log_{10}$ transformed titers, with subsequent back-transformation.

Reverse Cumulative Distribution Curves

The immune response profiles for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains in the aQIV and QIV groups in the FAS Immunogenicity were provided within the application.

For the A/H1N1 strain, the RCD curve for the aQIV group was shifted to the right relative to that for the QIV group, suggesting a greater magnitude of immune response for this strain in the aQIV group.

- **Ancillary analyses**

Immunogenicity Results by Age

For both the 50 to 59 years and 60 to 64 years age subgroups, the results were consistent with the overall study results in that the Day 22 immune response was observed to be higher for the A/H1N1 strain and there were no notable differences for the B strains for the aQIV group compared with the QIV group.

For the A/H3N2 strain, the point estimates of the Day 22 GMT ratios for both age subgroups were similar to those observed in the overall study population; however, the 95% CIs were wider due to the smaller sample sizes and cross the value of 1.

Immunogenicity Results by Previous Vaccination History

For subjects who had received an influenza vaccination within the previous 3 influenza seasons, the results were consistent with the overall study results in that the Day 22 immune response was observed to be higher for the A/H1N1 strain and there were no notable differences for the other 3 strains (A/H3N2 and B strains) for the aQIV group compared with the QIV group.

In contrast, for subjects who had not received an influenza vaccination within the previous 3 influenza seasons (see next Table): The Day 22 immune response was observed to be higher for the A/H1N1 (GMTr: 0.77 [0.67, 0.87]) and A/H3N2 (GMTr: 0.80 [0.68, 0.94]) strains for the aQIV group compared with the QIV group.

There were no notable differences in immunogenicity at Day 22 for aQIV versus QIV for the B/Yamagata or B/Victoria strains.

Table 47: Post-vaccination GMT, GMT ratio, and analysis of superiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at day 22 by HI assay by influenza vaccination history (FAS immunogenicity)

	Received at least one influenza vaccination within the previous 3 influenza seasons			Did not receive any influenza vaccination within the previous 3 influenza seasons		
	Day 22 GMT		GMT Ratio	Day 22 GMT		GMT Ratio
	aQIV N=586 (95% CI)	QIV N=598 (95% CI)	QIV over aQIV (95% CI)	aQIV N=441 (95% CI)	QIV N=418 (95% CI)	QIV over aQIV (95% CI)
A/H1N1	649.30 (601.96, 700.37)	546.68 (507.95, 588.37)	0.84 (0.76, 0.93)	759.44 (691.44, 834.13)	581.38 (527.53, 640.73)	0.77 (0.67, 0.87)
A/H3N2	279.20 (257.32, 302.93)	284.32 (262.71, 307.72)	1.02 (0.91, 1.14)	389.39 (347.50, 436.32)	311.96 (277.50, 350.70)	0.80 (0.68, 0.94)
B/Yamagata	116.36 (110.51, 122.52)	110.10 (104.72, 115.76)	0.95 (0.88, 1.01)	188.89 (172.31, 207.07)	178.81 (162.69, 196.52)	0.95 (0.83, 1.08)
B/Victoria	102.07 (96.65, 107.78)	102.05 (96.81, 107.58)	1.00 (0.93, 1.08)	184.80 (168.11, 203.16)	186.45 (169.13, 205.56)	1.01 (0.88, 1.15)

Source: Table 14.2.1.1.2.1.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; FAS = Full Analysis Set; GMT = geometric mean titer; HI = hemagglutination inhibition; QIV = Quadrivalent Influenza Vaccine; UL = upper limit.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Adjusted analysis GMT model: $\log_{10}$ transformed postvaccination (Day 22) HI titer = vaccine group + age cohort + sex+ prevaccination titer ($\log_{10}$ transformed), with subsequent back-transformation.

Immunogenicity Results by Sex

For both the male and female subgroups, the results were consistent with the overall study results in that the Day 22 immune response was observed to be higher for the A/H1N1 strain and there were no notable differences for the other 3 strains (A/H3N2 and B strains) for the aQIV group compared with the QIV group.

Immunogenicity Results by Race

For White subjects, the results were consistent with the overall study results in that the Day 22 immune response was observed to be higher for the A/H1N1 strain, the point estimate of the Day 22 GMT ratio for the A/H3N2 strain was similar to that observed in the overall study population (however, the 95% CIs were wider due to the smaller sample sizes and crossed the value of 1), and there were no notable differences for the B strains for the aQIV group compared with the QIV group.

For Black or African American subjects and subjects in the "Other" (including American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander and Other) race category, the small numbers of subjects in these two race categories (75 and 15 subjects, respectively) for these analyses limit any conclusion for these observations.

Immunogenicity Results by Ethnicity

For subjects in the category of "Not Hispanic or Latino" ethnicity the results were consistent with the overall study results in that the Day 22 immune response was observed to be higher for the A/H1N1 strain, the point estimate of the Day 22 GMT ratio and the UL of the 95% CI for the H3N2 strain were similar to that observed in the overall study population, and there were no notable differences for the B strains for the aQIV group compared with the QIV group.

For subjects of Hispanic or Latino ethnicity, the small number of subjects in this ethnicity category (26 subjects) for these analyses limits any conclusion for these observations.

Immunogenicity Results by Comorbidity Risk Score

For subjects with a comorbidity score <50 the results were consistent with the overall study results in that the Day 22 immune response was observed to be higher for the A/H1N1 strain and there were no notable differences for the other 3 strains (A/H3N2 and B strains) for the aQIV group compared with the QIV group (see Table 48).

In contrast, for subjects with a comorbidity risk score ≥50: The Day 22 immune response was observed to be higher for both A strains (GMTr [95% CI]: A/H1N1 – 0.73 [0.57, 0.93] and A/H3N2 – 0.73 [0.55, 0.98]) and the B/Yamagata (GMTr [95% CI]: 0.77 [0.64, 0.94]) strain for the aQIV group compared with the QIV group.

There were no notable differences in immunogenicity at Day 22 for aQIV versus QIV for the B/Victoria strain.

Table 48: Post-vaccination GMT, GMT ratio, and analysis of superiority of aQIV relative to QIV in subjects 50 to 64 years of age for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria at Day 22 by HI assay by comorbidity risk score (FAS immunogenicity)

	Comorbidity Risk Score <50			Comorbidity Risk Score ≥50		
	Day 22 GMT		GMT Ratio	Day 22 GMT		GMT Ratio
	aQIV N=912 (95% CI)	QIV N=918 (95% CI)	QIV over aQIV (95% CI)	aQIV N=115 (95% CI)	QIV N=98 (95% CI)	QIV over aQIV (95% CI)
A/H1N1	720.39 (676.42, 767.21)	586.26 (550.47, 624.37)	0.81 (0.75, 0.89)	789.34 (659.78, 944.34)	576.37 (475.63, 698.44)	0.73 (0.57, 0.93)
A/H3N2	337.24 (313.85, 362.36)	316.09 (294.36, 339.42)	0.94 (0.85, 1.03)	453.60 (368.59, 558.20)	333.16 (265.15, 418.62)	0.73 (0.55, 0.98)
B/Yamagata	150.15 (142.34, 158.39)	145.97 (138.42, 153.92)	0.97 (0.90, 1.05)	198.10 (172.89, 227.00)	153.05 (131.91, 177.58)	0.77 (0.64, 0.94)
B/Victoria	139.94 (132.30, 148.02)	141.89 (134.19, 150.03)	1.01 (0.94, 1.10)	172.85 (149.53, 199.80)	158.02 (135.26, 184.62)	0.91 (0.75, 1.12)

Source: Table 14.2.1.1.2.1.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CI = confidence interval; FAS = Full Analysis Set; GMT = geometric mean titer; HI = hemagglutination inhibition; QIV = Quadrivalent Influenza Vaccine; UL = upper limit.

Note 1: Immunogenicity was measured by HI assay using the following egg-derived target viruses: A/Victoria/2570/2019 (IVR-215) (A/H1N1), A/Cambodia/e0826360/2020 (IVR-224) (A/H3N2), B/Phuket/3073/2013 (BVR-1B) (B/Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (B/Victoria lineage).

Note 2: Adjusted analysis GMT model: $\log_{10}$ transformed postvaccination (Day 22) HI titer = vaccine group + age cohort + sex + influenza vaccination history+ prevaccination titer ($\log_{10}$ transformed), with subsequent back-transformation.

Immunogenicity Results by Baseline HI titre

For subjects with a baseline titre ≥1:10, the results were consistent with the overall study results in that the Day 22 immune response was observed to be higher for the A/H1N1 strain for the aQIV group compared with the QIV group and there were no notable differences in immunogenicity at Day 22 for aQIV versus QIV for the other 3 strains (A/H3N2 and B strains).

In contrast, for subjects with a baseline HI titre <1:10:

- The Day 22 immune response was observed to be higher for the A/H1N1 strain (GMTr [95% CI]: 0.59 [0.45, 0.77]) for the aQIV group compared with the QIV group.

- The point estimate of the Day 22 GMT ratio for the A/H3N2 strain (0.76) was lower than that observed in the overall study population (0.91), but the 95% CI was wider due to the smaller sample size and crossed the value of 1.
- There were no notable differences in immunogenicity at Day 22 for aQIV versus QIV for the B/Yamagata or B/Victoria strains.

- **Summary of main efficacy results**

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

Table 49: Summary of efficacy for trial V118_23

Title: A phase 3 randomised, observer-blind, controlled, multicentre clinical study to evaluate the immunogenicity and safety of an MF-59-adjuvanted vaccine in comparison with a licensed quadrivalent vaccine in adults 50 to 64 years of age.			
Study identifier	V118_23		
Design	Immunogenicity, Persistence of immune response, reactogenicity, and safety of the two vaccines were also assessed in this trial.		
	Duration of main phase:		The study duration was approximately 9 months for each subject. The study was conducted over the Northern Hemisphere 2021/2022 influenza season.
Hypothesis	Non-inferiority and Superiority		
Treatments groups	aQIV		Treatment: one dose of a MF-59-adjuvanted quadrivalent vaccine. Number randomised: 1027 subjects 50-64 years of age
	QIV		Treatment: one dose of a commercial non-adjuvanted quadrivalent vaccine; Fluarix Tetra (GSK) approved by CHMP. <number randomised: 1017 subjects 50-64 years of age
Endpoints and definitions: Only if the non-inferiority objectives were achieved, would the superiority objectives be tested. Only after the primary objectives were reached, would the secondary objectives be tested sequentially. All primary endpoint analyses were carried out with a one-sided alpha of 0.025 for each comparison.	Co-Primary endpoint 1a	To demonstrate Non-inferiority (of aQIV versus a nonadjuvanted quadrivalent influenza comparator (QIV)	As measured by hemagglutination inhibition (HI) GMTs and SCRs (seroconversion rates) for each vaccine strain, at 3 weeks after vaccination
	Co-Primary endpoint 1b	To demonstrate Superiority (aQIV induces a superior immune response compared with QIV)(first analysis)	As measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains.

	Co-Primary endpoint 1bis post-hoc	To demonstrate Superiority (aQIV induces a superior immune response compared with QIV)(post-hoc, more serum samples analysed than in 1b	As measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains.
	Secondary 2a	To demonstrate that aQIV induces a superior immune response compared with QIV	As measured by HI GMT for at least one vaccine strain at 3 weeks after vaccination.
	Secondary 2b	To demonstrate a greater persistence of the immune response for at least one vaccine strain at 6 months after vaccination with aQIV compared with QIV	As measured by HI GMT.
Database lock	9 September 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) Immunogenicity: All subjects in the All Enrolled Set who were randomised, received study vaccination and provided immunogenicity data at any time point. Used for primary analysis 1b, and for all secondary analysis Per Protocol Set (PPS) Immunogenicity: All subjects in the FAS Immunogenicity who: Had both Day 1 and Day 22 immunogenicity assessment; Correctly received the vaccine; Had no protocol deviations leading to exclusion and were not excluded due to other reasons defined prior to unblinding or analysis. Used for non-inferiority analysis 1a.		

<table>
<tr><td>Descriptive statistics and estimate variability</td><td colspan="3">
<table>
<tr><th></th><th colspan="2">Day 22 GMT</th></tr>
<tr><th></th><th>aQIV
N=983
(95% CI)</th><th>QIV
N=983
(95% CI)</th></tr>
<tr><td>A/H1N1</td><td>735.20 (692.28, 780.78)</td><td>587.24 (552.90, 623.70)</td></tr>
<tr><td>A/H3N2</td><td>347.75 (324.63, 372.53)</td><td>314.38 (293.54, 336.70)</td></tr>
<tr><td>B/Yamagata</td><td>154.40 (146.79, 162.41)</td><td>145.72 (138.56, 153.26)</td></tr>
<tr><td>B/Victoria</td><td>144.35 (136.89, 152.21)</td><td>143.59 (136.21, 151.37)</td></tr>
<tr><th></th><th colspan="2">Day 22 SCR</th></tr>
<tr><th></th><th>aQIV
N=983
% (95% CI)</th><th>QIV
N=983
% (95% CI)</th></tr>
<tr><td>A/H1N1</td><td>81.0 (78.37, 83.43)</td><td>76.5 (73.64, 79.10)</td></tr>
<tr><td>A/H3N2</td><td>63.4 (60.26, 66.46)</td><td>61.6 (58.44, 64.67)</td></tr>
<tr><td>B/Yamagata</td><td>43.2 (40.09, 46.43)</td><td>41.1 (37.96, 44.23)</td></tr>
<tr><td>B/Victoria</td><td>44.3 (41.10, 47.46)</td><td>40.7 (37.64, 43.89)</td></tr>
</table>
</td></tr>
<tr><td rowspan="6">Effect estimate per comparison</td><td rowspan="2">Co-Primary endpoint 1a</td><td>Comparison groups:
QIV vs aQIV</td><td>GMT ratio (QIV/aQIV) and SCR (QIV –aQIV)</td></tr>
<tr><td>Non-inferiority will be demonstrated if the upper limit (UL) of the 95% confidence interval (CI) for the inter-group GMT ratio (QIV/aQIV) is ≤1.5 for each vaccine strain, and the
UL of the 95% CI for the difference in SCR2 (QIV – aQIV) is ≤10% for each vaccine strain.</td><td>
<table>
<tr><th></th><th colspan="2">GMT Ratio</th></tr>
<tr><th></th><th>QIV over aQIV
(95% CI)</th><th>Met predefined noninferiority criteria?</th></tr>
<tr><td>A/H1N1</td><td>0.80 (0.74, 0.87)</td><td>Yes</td></tr>
<tr><td>A/H3N2</td><td>0.90 (0.82, 0.99)</td><td>Yes</td></tr>
<tr><td>B/Yamagata</td><td>0.94 (0.88, 1.01)</td><td>Yes</td></tr>
<tr><td>B/Victoria</td><td>0.99 (0.92, 1.07)</td><td>Yes</td></tr>
<tr><th></th><th colspan="2">SCR Difference</th></tr>
<tr><th></th><th>QIV minus aQIV
% (95% CI)</th><th>Met predefined noninferiority criteria?</th></tr>
<tr><td>A/H1N1</td><td>-4.5 (-8.20, -0.89)</td><td>Yes</td></tr>
<tr><td>A/H3N2</td><td>-1.8 (-6.12, 2.52)</td><td>Yes</td></tr>
<tr><td>B/Yamagata</td><td>-2.2 (-6.56, 2.22)</td><td>Yes</td></tr>
<tr><td>B/Victoria</td><td>-3.5 (-7.91, 0.87)</td><td>Yes</td></tr>
</table>
</td></tr>
<tr><td rowspan="2">Co-Primary endpoint 1b</td><td>Comparison groups:
QIV over aQIV</td><td>GMT ratio (QIV/aQIV)</td></tr>
<tr><td>Superior immune response will be demonstrated if the UL of the 95% CI for the intergroup
GMT ratio (QIV/aQIV) is <1.0 for at least 2 of the 4 vaccine strains.</td><td>
<table>
<tr><th colspan="2">GMT Ratio</th></tr>
<tr><th>QIV over aQIV
(95% CI)</th><th>Met predefined superiority criteria?</th></tr>
<tr><td>A/H1N1 0.80 (0.74, 0.87)</td><td>Yes</td></tr>
<tr><td>A/H3N2 0.91 (0.83, 1.002)</td><td>No</td></tr>
<tr><td>B/Yamagata 0.95 (0.88, 1.01)</td><td>No</td></tr>
<tr><td>B/Victoria 1.00 (0.93, 1.08)</td><td>No</td></tr>
</table>
</td></tr>
<tr><td rowspan="2">Co-Primary endpoint 1bis</td><td>Comparison groups:
QIV over aQIV</td><td>GMT ratio (QIV/aQIV)</td></tr>
<tr><td>Superior immune response will be demonstrated if the UL of the 95% CI for the intergroup
GMT ratio (QIV/aQIV) is <1.0 for at least 2 of the 4 vaccine strains.</td><td>
<table>
<tr><th colspan="2">GMT Ratio</th></tr>
<tr><th>QIV over aQIV
(95% CI)</th><th>Met predefined superiority criteria?</th></tr>
<tr><td>A/H1N1</td><td>0.81 (0.74, 0.88)</td><td>Yes</td></tr>
<tr><td>A/H3N2</td><td>0.91 (0.83, 0.998)</td><td>Yes</td></tr>
<tr><td>B/Yamagata</td><td>0.95 (0.88, 1.01)</td><td>No</td></tr>
<tr><td>B/Victoria</td><td>1.00 (0.93, 1.07)</td><td>No</td></tr>
</table>
</td></tr>
<tr><td>Notes</td><td colspan="3">The Co-primary endpoint 1 bis was an analysis performed by the applicant including additional serum samples (less than 50) as compared to the analysis described for endpoint 1b. This analysis was made after knowing the results for the endpoint 1b.</td></tr>
<tr><td>Analysis description</td><td colspan="3">Secondary analysis</td></tr>
</table>

	The secondary analyses were not performed since additional testing stopped after the success criterion for endpoint 1b was not met.

2.5.5.3. Supportive studies

This section summarises immunogenicity results from the 7 supportive studies that compare immunogenicity of a single dose of aTIV versus TIV (V7P3, V7P5, V7P7, V7P8, V7P25 V7P35, V104P3). There were also two open label non-interventional studies comparing aTIV versus TIV, which were not sponsored by the applicant (C70P1 and V70_49OBTP). The summary provided for each study was 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 post-vaccination against homologous or heterologous strains, antibody persistence at 6 months post-vaccination, immunogenicity (homologous or heterologous strains) as determined by microneutralisation (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 hospitalisations for influenza disease or pneumonia (C70P1 conducted in Italy) and to assess vaccine effectiveness for influenza disease (V70_49OBTP conducted Canada).

The HI results of these supportive studies are summarised:

- V7P3 was a Phase 2, prospective, randomised, parallel, observer blind study to evaluate the safety, tolerability and immunogenicity of aTIV versus TIV (Agrippal) administered to subjects ≥65 years of age/

  aTIV, elicited higher HI GMTs than TIV for all 3 strains 28 days post-vaccination (189 vs. 149 for A/H3N2, 45 vs. 31 for A/H1N1, and 115 vs. 74 for B in the aTIV vs. TIV groups, respectively); the difference between vaccine groups was statistically significant for the B strain (P = 0.012). aTIV met all 3 CHMP criteria for all 3 strains, while TIV met the criteria for A/H3N2 and B strains and did not meet the criterion for the A/H1N1 strain.

- V7P5 was a Phase 2, observer-blind, randomised, single-centre study to evaluate the safety, tolerability and immunogenicity of aTIV supplied in a single syringe versus aTIV supplied in separate vial versus TIV (Agrippal) administered to subjects ≥65 years of age.

  TIV (single syringe) induced statistically significantly higher HI titres than TIV for all 3 antigens (GMTr [aTIV/TIV] = 1.83 [95% CI 1.31, 2.54]) for H3N2, 1.56 [95% CI 1.18, 2.06] for H1N1, and 1.71 [95% CI 1.33, 2.21] for B), and exhibited immune responses that were consistently similar to or higher than the admixed (single vial) aTIV formulation. Both aTIV formulations met all 3 CHMP criteria for each strain.

- V7P7 was a Phase 2, observer-blind, randomised, multicentre, parallel study to evaluate the tolerability and immunogenicity (with clinical surveillance for efficacy in a subset of subjects) of aTIV versus TIV (Agrippal) administered to subjects ≥65 years of age.

  Post-vaccination GMTs were similar in the two groups (107 vs. 91 for B, 286 vs. 246 for A/H3N2, and 200 vs. 197 for A/H1N1 in the aTIV versus TIV groups. Both vaccines met all CHMP criteria 28 days post-vaccination in this previously unvaccinated population. The aTIV

group tended to elicit higher responses for all parameters, but none of these differences was statistically significant.

- V7P8 was a Phase 2, multicentre, observer-blind, parallel study to evaluate the safety, tolerability, and immunogenicity of aTIV versus TIV (Agrippal) administered to subjects ≥65 years of age.

  aTIV group elicited significantly higher post-vaccination GMTs than the TIV group for both the A/H3N2 (GMT = 103 vs. 55 respectively) and B strains (GMT = 102 vs. 70, respectively) (P < .001). The magnitudes of the GMRs and SCRs for all 3 strains were also significantly higher in the aTIV vs. TIV groups.

- V7P25 was a Phase 2, observer-blind, randomised, multicentre, parallel study to evaluate the safety, tolerability and immunogenicity of aTIV versus TIV (Vaxigrip) administered to subjects ≥65 years of age.

  GMTs 28 days post-vaccination were similar in both groups (556 vs. 545 for A/H1N1, 431 vs. 437 for A/H3N2 and 554 vs. 468 for B in the aTIV and TIV groups, respectively. Both vaccines elicited similar responses to all 3 strains 28 days post-vaccination; the results for each group met all 3 CHMP criteria for each strain; none of the differences between the 2 groups were statistically significant.

- V7P35 was Phase 4, single blind, multicentre, parallel study to evaluate the safety and effectiveness of aTIV vs TIV (Influvac) administered to subjects ≥65 years of age.

  In the primary immunogenicity endpoint analysis, HI GMTs at 28 days post-vaccination were similar in both vaccine groups (227 vs. 192 for A/H1N1, 272 vs. 250 for A/H3N2 and 150 vs. 130 for B strains) in the aTIV and TIV groups, respectively. aTIV was consistently more immunogenic than TIV in terms of both GMRs and SCR.

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.

Study C70P1

Study C70P1 was a non-interventional 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 hospitalisations for influenza or pneumonia during the influenza season amongst subjects ≥65 years of age who received either aTIV or non-

adjuvanted 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 immunisation 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 hospitalisation 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 hospitalisation 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 non-interventional study using a test-negative design to estimate vaccine effectiveness of aTIV versus a non-adjuvanted 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 analysed 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 non-adjuvanted 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.

MF59-adjuvanted Influenza Vaccine and 23-valent Pneumococcal Polysaccharide Vaccine

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 randomised 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.

Immunogenicity and Safety of PCV13 and Fluad in Adults Aged ≥60 Years

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 randomised 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.

V7P38, V70P3 and Baldo *et al*

Specifically, to support of the benefit of the adjuvanted influenza vaccine in subjects from 50 to 64 yoa, results from three RCT were provided: V7P38 (sponsored by Chiron vaccines), V70P3 (sponsor unknown), and a trial sponsored by a Public Health Italian academic group.

In these three studies, immunogenicity results (in terms of HAI titres) obtained in subjects vaccinated with an MF-59 adjuvanted egg-based trivalent vaccine (aTIV) are compared to those reached following administration of a nonadjuvanted egg-based trivalent influenza vaccine (TIV). The studies were conducted in three different influenza seasons (NH 2000/01, NH 2006/07 and NH 2005/06). Study V7P38 included subjects from 50 to 64 yoa; V70P3 recruited subjects from 18 to 60 yoa, and the applicant provided the immunogenicity results for the age subgroup 50 to 60 years; and the study from Baldo et al, included subjects from 18 to 60 yoa [mean age 51 y (standard deviation ± 12 y)]. No age subgroup analysis from this latter study is provided. Consistently, in the three studies a higher immune response (in terms of GMTs), against all three viral components, was observed for the adjuvanted vaccine as compared to the non-adjuvanted one. Moreover, this increase in GMT was statistically significant [i.e., the upper limit of the 95%CI of the GMTR (TIV vs aTIV) was lower than 1] for the three strains in trial V70P3 and for two strains in trial V7P38 and in the study by Baldo et al[1].

[1] Baldo V, Baldovin T, Floreani A, Carraro AM, Trivello R; Family Medicine Group of Pianiga. MF59-adjuvanted influenza vaccine confers superior immunogenicity in adult subjects (18-60 years of age) with chronic diseases who are at risk of post-influenza complications. Vaccine. 2007 May 16;25(20):3955-61. doi: 10.1016/j.vaccine.2007.02.045. Epub 2007 Mar 6. PMID: 17383057.

Table 50: Study V7P38 – day 0 and day 21 GMTs and day 21 GMT ratios in subjects 50 to 64 years of age (post-dose immunogenicity set)

	Adjusted Day 0 GMT		Adjusted Day 21 GMT		Day 21 GMT Ratio
Strain	aTIV N=93 (95% CI)	TIV N=96 (95% CI)	aTIV N=93 (95% CI)	TIV N=96 (95% CI)	TIV over aTIV (95% CI)
Influenza A/H1N1/New Caledonia/20/1999 egg ab	41.93 (34.44, 51.05)	40.97 (33.77, 49.69)	373.68 (297.90, 468.73)	319.99 (256.15, 399.73)	0.86 (0.64, 1.14)
Influenza A/H3N2 Moscow/10/1999 egg ab	38.62 (27.44, 54.35)	34.00 (24.31, 47.55)	609.66 (444.79, 835.64)	336.83 (247.16, 459.02)	0.55 (0.37, 0.82)
Influenza B Beijing/184/1993 egg ab	42.80 (32.03, 57.20)	35.56 (26.75, 47.27)	447.18 (347.69, 575.15)	322.64 (252.01, 413.06)	0.72 (0.53, 0.99)

Source: Study V7P38 Table 2.1.1.

Abbreviations: aTIV = adjuvanted egg-based Trivalent Influenza Vaccine; CI = confidence interval; GMT = geometric mean titre; TIV = nonadjuvanted egg-based Trivalent Influenza Vaccine.

Note 1: GMT ratio TIV vs aTIV post-vaccination.

Table 51: Study V70P3 – day 1 and day 22 GMTs and day 22 GMT ratios in subjects 50 to 60 years of age (full analysis set)

		Adjusted Day 1 GMT		Adjusted Day 22 GMT		Day 22 GMT Ratio
Strain	Homologous/ Heterologous	aTIV N=114 (95% CI)	TIV N=109 (95% CI)	aTIV N=114 (95% CI)	TIV N=109 (95% CI)	TIV over aTIV (95% CI)
Influenza A/H1N1/New Caledonia/1999 egg ab	Homologous	14.42 (11.11, 18.71)	15.79 (12.12, 20.56)	141.81 (104.06, 193.25)	79.73 (57.83, 109.93)	0.56 (0.36, 0.88)
Influenza A/H1N1/Solomon/2006 egg ab	Heterologous	9.64 (7.73, 12.01)	9.84 (7.85, 12.34)	53.79 (39.51, 73.25)	37.01 (27.14, 50.46)	0.69 (0.44, 1.07)
Influenza A/H3N2/Wisconsin/2005 egg ab	Homologous	16.66 12.61, 22.02)	12.24 (9.21, 16.28)	413.61 (306.33, 558.47)	199.60 (146.18, 272.55)	0.48 (0.31, 0.74)
Influenza A/H3N2/New York/2004 egg ab	Heterologous	31.94 (22.60, 45.14)	24.41 (17.14, 34.76)	743.79 (542.55, 1019.65)	363.40 (263.56, 501.05)	0.49 (0.31, 0.77)
Influenza B/Malaysia/2004 egg ab	Homologous	5.98 (5.49, 6.52)	5.75 (5.26, 6.28)	39.36 (30.68, 50.49)	21.97 (17.03, 28.34)	0.56 (0.39, 0.80)
Influenza B/Jiangsu/2003 ab	Heterologous	10.06 (8.33, 12.15)	8.78 (7.25, 10.63)	43.05 (33.31, 55.64)	28.10 (21.65, 36.49)	0.65 (0.45, 0.94)

Source: Study V70P3 Table 2.1.2.

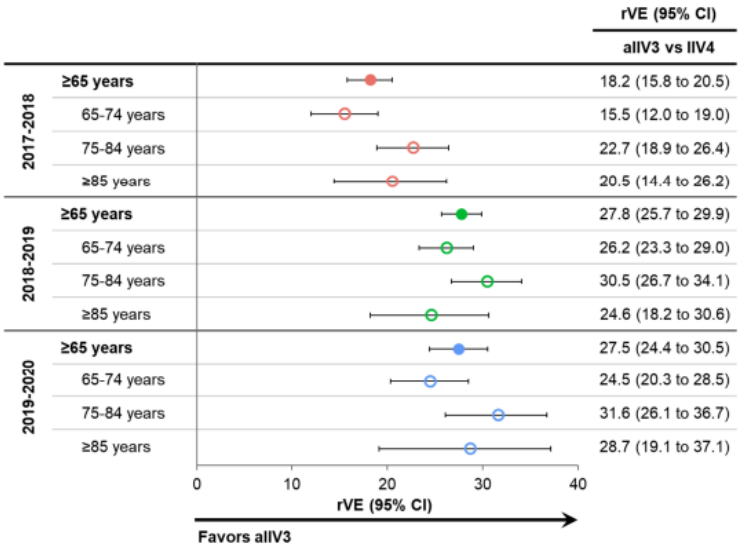
Abbreviations: aTIV = adjuvanted egg-based Trivalent Influenza Vaccine; CI = confidence interval; GMT = geometric mean titre; TIV = nonadjuvanted egg-based Trivalent Influenza Vaccine.

Note 1: GMT ratio TIV vs aTIV post-vaccination.

Effectiveness studies

The applicant also provided results from three vaccine effectiveness studies: two retrospective cohort studies sponsored by Seqirus (described by Boikos et al. 2021, and Imran et al. 2022), and one public health surveillance study carried out by the United Kingdom Health Security Agency (UKHSA). The two retrospective cohort studies were conducted during the NH 2017/2018, 2018/2019, and 2019/2020 influenza seasons to estimate the relative vaccine effectiveness of adjuvanted egg-based trivalent influenza vaccine (aTIV) versus a nonadjuvanted egg-based standard-dose quadrivalent influenza vaccine (QIV) or versus a nonadjuvanted egg-based high-dose trivalent influenza vaccine (HD-TIV) in preventing influenza-related medical encounters (IRMEs) in individuals ≥65 years of age. The two studies used the same USA integrated dataset comprising de-identified (anonymous) data from electronic medical records from primary care and specialty clinics linked with pharmacy and medical claims. The applicant described vaccine effectiveness results particularly for the age group 65 to 74 years, which is the closest one to the sought age indication of 50 to 64 years. In these studies, the relative vaccine effectiveness of aTIV vs QIV for the prevention of influenza-related medical encounters significantly favoured aTIV in the overall study population (≥65 years of age). Specifically, for the 65-74 years age subgroup, a benefit was observed for aTIV compared with QIV, with the relative vaccine effectiveness ranging from 15.5% (95% CI: 12.0 to 19.0) to 26.2% (95% CI: 23.3 to 29.0) across the

2017-2020 influenza seasons. Similarly, for the age subgroup of 65-74 years, aTIV demonstrated a higher or comparable benefit to a HD-TIV in the 3 influenza seasons.

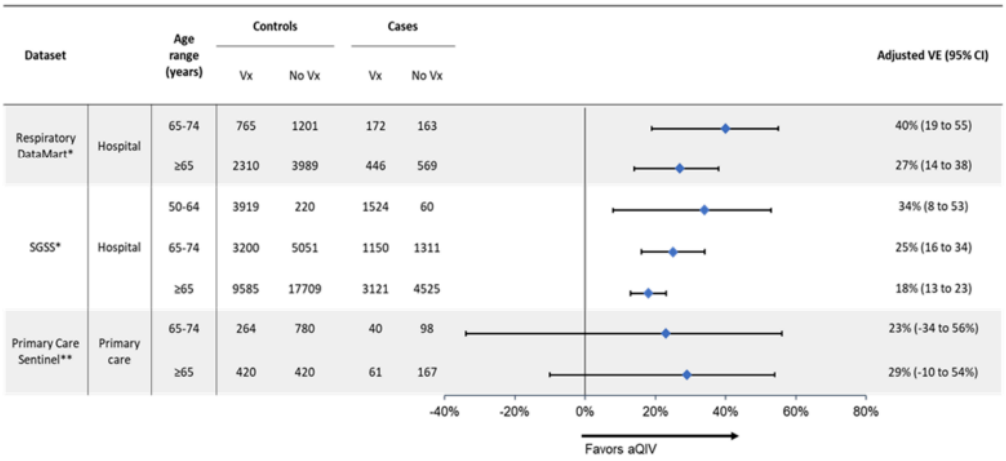


Abbreviations: aIIV3 (aTIV) = adjuvanted egg-based Trivalent Influenza Vaccine; CI = confidence interval; IIV4 (QIV) = nonadjuvanted egg-based standard-dose Quadrivalent Influenza Vaccine: rVE = relative vaccine effectiveness.

Figure 5: Relative vaccine effectiveness of aTIV (aIIV3) vs QIV (IIV4) for the prevention of influenza-related medical encounters during the 3 influenza seasons between 2017 and 2020 in subjects ≥65 years of age and by age subgroup (65-74 years, 75-84 years, and ≥85 years).

Vaccine effectiveness data from the MF-59 adjuvanted quadrivalent vaccine (aQIV) based on RT-PCR confirmed influenza cases were provided in the study carried out by the UKHSA during the NH 2022/2023 influenza season. The study analysed vaccine effectiveness of aQIV against influenza hospitalisation and against influenza disease (based on data from primary care sentinel surveillance system). Two sources of laboratory-confirmed influenza hospital outcomes were used (the respiratory DataMart and the Second generation Surveillance System –SGSS-). This study provides data on prevention of hospitalisation not only for the 65-74 years of age group but also for the age group 50 to 64 yoa. These latter data appear to derive from adults aged 50-64 that received aQIV off label and outside of national recommendations.

Data from primary care sentinel surveillance systems showed an adjusted vaccine effectiveness against outpatient laboratory-confirmed influenza of 23% (95% CI: -34 to 56) in the 65-74 years age group. Since the % CI includes zero, these data do not show evidence of vaccine effectiveness in that particular season. However, using the outcome of laboratory-confirmed influenza hospitalisation, the adjusted vaccine effectiveness for aQIV was 40% (95% CI: 19 to 55) (data from the Respiratory DataMart system) and 25% (95% CI: 16 to 34) (data from the SGSS) in the 65-74 years age group. Results from the SGSS for the 50-64 years age group also demonstrated an adjusted vaccine effectiveness for aQIV against laboratory-confirmed influenza hospitalisation of 34% (95% CI: 8 to 53). Although the study made by the UKHSA does not compare an adjuvanted vs a nonadjuvanted vaccine, the results obtained show significant vaccine effectiveness of aQIV against laboratory-confirmed influenza hospitalisation in the 50-64 and in the 65-74 years of age group.



Abbreviations: aQIV = adjuvanted egg-based Quadrivalent Influenza Vaccine; aVE = absolute vaccine effectiveness; CI = confidence interval; NH = Northern Hemisphere; PHE = Public Health England; SGSS = Second Generation Surveillance System; VE = vaccine effectiveness; Vx = vaccinated with aQIV.
*Adjusted for week of swab (spline), PHE region, age group (≥65 years only), clinical risk status, COVID-19 vaccination status (aVE for prevention of laboratory-confirmed influenza hospitalisation).
**Adjusted for week of swab (spline), age group (≥65 years only), clinical risk status, scheme (aVE for prevention of outpatient laboratory-confirmed influenza).

Figure 6: Absolute vaccine effectiveness of aQIV for the prevention of laboratory-confirmed influenza hospitalisation or outpatient laboratory-confirmed influenza in subjects ≥50 years (NH 2022/2023 influenza season)

Paediatric data

V118_05: Study V118_05 was a Phase 3, observer-blind, stratified, randomised, 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)

A total of 10,644 subjects ≥6 to <72 months of age were enrolled/randomised 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.

Three vaccines were used in the trial:

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 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.

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.

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.

Vaccine efficacy was assessed for the prevention of first-occurrence laboratory confirmed influenza associated with symptomatic influenza-like illness (ILI). Influenza-like illness was defined as fever of 37.8°C or above along with any of the following: cough, sore throat, nasal congestion, or runny nose occurring at ≥ 21 days and ≤ 180 days after the last vaccination or until the end of the influenza season, whichever was longer.

5,352 children were enrolled in the Fluad Tetra group and 5,292 children in the non-adjuvanted comparator vaccine group.

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). 10 during season one and 498 during season two.

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 52: 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.

The majority of influenza cases were A/H3N2. Based on antigenic typing, more than ninety percent of A/H3N2 strains from season two were determined to be antigenically distinct from egg-propagated A/Texas/50/2012, the H3N2 vaccine strain.

Relative vaccine efficacy: RT-PCR-confirmed influenza by strain was determined as a secondary endpoint. 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 53: 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).

A subset of children enrolled in this study was evaluated for their immunological response to Fluad Tetra and the non-adjuvanted comparator. Immunogenicity assessments were performed prior to (each) vaccination and 3 weeks after the last vaccination. A total of 2886 children were included in the subset for immunogenicity evaluation (Fluad Tetra: N=1481; non-adjuvanted comparator vaccine: N=1405).

The GMTs and percentage of subjects with seroconversion at 21 days after last vaccination are reported for homologous strains in the tables below, 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 54: Geometric mean HI titres, 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

	Strains[b]	aQIV N=1481	Comparator[a] N=1405	GMT ratio (95% CI)
Strain[b]		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 55: 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).

Fluad Tetra demonstrated a higher immune response compared to the non-adjuvanted comparator vaccine. In addition, in children naïve to influenza vaccination antibody titres 4 weeks after the first vaccination as well as 3 weeks after the second vaccination were greater in subjects who received Fluad Tetra.

At 12 months post-vaccination, persistence of the immune response was higher in the Fluad Tetra group compared to the non-adjuvanted comparator group.

2.5.6. Discussion on clinical efficacy

The proposed indication for aTIV is prophylaxis of influenza in adults 50 years of age and older. As the manufacturing process and formulation of aTIV and aQIV (Fluad Tetra) are the same, with the exception of an additional B strain included in aQIV, data from clinical studies with aQIV are included to support efficacy and immunogenicity of aTIV.

It should be noted that aTIV has been already authorised in several EU member states through the MRP under the name of Chiromas/Fluad since 1997.

Dose response studies

The vaccine dose and dosing schedule of aQIV and aTIV are considered appropriate. In both studies, the addition of the adjuvant led to an increase in immune response, but also to an increase of reactogenicity.

Clinical efficacy/immunogenicity data supporting the use of aTIV in individuals 65 years of age and older

Study V70_27 was a randomised 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. The study included adults aged ≥65 years of age. Randomisation was stratified by age with 65 to 74 years versus ≥75 years, while the protocol pre-specified 65 to 75 years versus >75 years. The design of the study was 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. 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%.

Non-inferiority of aTIV versus TIV for GMT ratios and differences in seroconversion for all 3 strains included in TIV in adults aged ≥65 years was demonstrated. The immune response of aTIV was consistently higher as compared to the response to TIV. However, according to the predefined superiority margins (GMTratio >1.5, SCR difference >10%) applied by the applicant, superiority could not be claimed. The estimated GMTr for the A/H1N1 strain, A/H3N2 strain and the B strain were 1.37, (95%CI: 1.29, 1.46) , 1.6 (95%CI: 1.51, 1.68) and 1.14 (95%CI: 1.08, 1.2), the estimated SCR difference was 9.6% (95%CI: 7.4%, 11.8%), 13.8% (95%CI: 11.7%, 16%) and 3% (95%CI: 1%, 5%) for A/H1N1, A/H3N2 and B strain, respectively. The relevance of the superiority margins applied by the applicant are not known. Furthermore, according to the guideline on influenza vaccines (non-clinical and clinical module) (EMEA/CHMP/VWP/164653/05 Rev. 1), statistical superiority would be sufficient. Therefore not meeting the superiority margins as defined by the applicant does not preclude drawing the conclusion that an immunological advantage of the adjuvant has been demonstrated. Considering the consistently higher response against homologous strains at D22 in addition the improved responses against heterologous influenza A strains, an immunological advantage of aTIV over TIV can be concluded.

There was no outspoken advantage in terms of persistence, as the response to aQIV was only substantial higher for A/H3N2 at D181, not for the other strains. Similarly, at D366, for the H3N2 strain a marginal difference in GMTr was observed, all other persistence results showed comparable results.

Analysis by subgroups such as age (65-75 vs. >75 years of age), underlying chronic conditions and baseline serology status showed that the immune response to aTIV was generally higher than that to TIV.

Study V118_20 allowed to bridge the data with the aTIV to the quadrivalent (aQIV) formulation, which contains an additional B strain and which was used to authorise aQIV. Study V118_20 was a randomised, double-blind, controlled 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 Victoria strain, and aTIV-2, containing the B Yamagata strain based upon the GMT ratio and SCR. The design of the study and predefined endpoints as well as margins was considered appropriate. The study included males and females aged ≥65 years of age who were healthy or were at high risk of complications from influenza.

Non-inferiority of the four strains of the aQIV compared to the corresponding strains in the aTIV was shown for GMT ratios as well as for SCR differences. This means that the additional B strain in aQIV did

not induce immune interference. Conversely, immunogenicity and efficacy/effectiveness data for aQIV are also considered relevant for aTIV.

V118_18 is a Phase 3, randomised absolute efficacy observer-blind, controlled, study to evaluate the efficacy, safety and immunogenicity of aQIV compared to non-influenza vaccine comparator (Boostrix) in 6790 individuals ≥65 years of age. The goal of this study was to demonstrate that aQIV prevents influenza in elderly. 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. The pre-specified success criterion to demonstrate VE of aQIV was not met. The majority of influenza cases were A/H3N2 strains and most of them (91%) were antigenically unmatched to the vaccine strain (12 out of 124 cases based on the protocol-defined ILI). Although the V118_18 study did not meet the primary and key secondary efficacy objectives, the study results showed reasonable protection during influenza seasons with an antigenic mismatch between the circulating and vaccine influenza strains.

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 Centres 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). In these analysis, the efficacy of aQIV was: 32.12% [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.

In summary, aQIV showed moderate vaccine efficacy against influenza in adults 65 years of age and above. 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).

The 7 supportive studies that compare immune response following aTIV versus TIV vaccination showed a generally higher antibody response with the adjuvanted vaccine. Therefore, all these data are in the same line than those observed in study V118_20. Both sets of data showed that the adjuvanted vaccine is more immunogenic than the non-adjuvanted comparator.

Regarding the revaccination studies, in general the results showed 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.

The previous approval of the aTIV at national level 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 was inferred by the higher antibody response that they trigger, noting that 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.

Clinical efficacy/immunogenicity data supporting the use of aTIV in individuals 50 to 64 years of age

Study V118_23 was a randomised, active controlled, observer-blind, multicentre study that aimed to evaluate the immunogenicity and safety of aQIV versus a licensed non-adjuvanted QIV comparator in subjects 50 to 64 years of age. The primary immunogenicity objectives were to demonstrate non-inferiority and superiority of aQIV versus a non-adjuvanted quadrivalent comparator vaccine based on the haemagglutinin antibody response. The study was conducted in the Northern Hemisphere 2021/2022 influenza season and enrolled 2044 adults aged 50 to 64 years, of whom 39% were male, and 58% received an influenza vaccine in the previous season. Characteristics were balanced between the treatment groups. Non-inferiority was demonstrated for both the GMT ratio (QIV/aQIV) for all four vaccine strains (A/H1N1: 0.87; A/H3N2: 0.99; B/Yamagata: 1.01; B/Victoria: 1.07) as well as for the SCR difference (QIV – aQIV; A/H1N1: -0.89%; A/H3N2: 2.52%; B/Yamagata: 2.22%; B/Victoria: 0.87%). Superiority could be claimed for the A/H1N1 strain but the predefined superiority criterion was not met for the B/Yamagata, B/Victoria (1.08) and the A/H3N2 strain therefore the prespecified success criterion for demonstrating a superior immune response for aQIV compared with QIV was not met in subjects 50 to 64 years of age.

When the analysis was performed in the FAS Immunogenicity (complete serology dataset), the UL of the 95% CI for the adjusted inter-group Day 22 GMT ratio was below the protocol specified superiority margin of 1.0 for two of the four strains [A/H1N1 (0.88) and A/H3N2 (0.998)]. Thus in this analysis, a superior immune response was observed for aQIV vs QIV for 2 of the 4 vaccine strains.

The sensitivity analysis performed in the PPS for immunogenicity (both the first analysis and the one performed in the complete serology dataset) demonstrated superiority of aQIV compared to QIV for two (A/H1N1 and A/H3N2) of the four vaccine strains.

In summary, the planned primary immunogenicity objective consisting of the two co-primary endpoints, 1a (the non-inferiority of the GMT ratio and the SCR difference for all strains in the PPS set), and 1b (the superiority in at least 2 out of 4 strains in the GMT ratio in the FAS population) was not fulfilled. Specifically, while the non-inferiority test for objective 1a achieved statistical significance, the superiority assessment of the GMT ratio was not met as only one strain (A/H1N1) fulfilled the predefined superiority criteria. Notably, as this co-primary objective was not met, any further testing did not maintain Type I error control and was therefore considered only exploratory. No confirmatory claims can be made from these tests. The applicant conducted a post-hoc sensitivity analyses based on the "Complete Serology Dataset", and then, and additional strain (A/H3N2) was shown to be significant. From a methodological and statistical point of view, this post-hoc sensitivity analysis cannot replace or rescue the main analysis, as there was no free alpha for confirmatory testing.

Overall, the subgroup analyses for the FAS Immunogenicity set regarding age, sex, race, ethnicity, previous vaccination history (received or not an influenza vaccination within the previous 3 influenza seasons) and comorbidity risk score were consistent with the overall study result. In fact, the Day 22 immune response was observed to be higher for the A/H1N1 strain for the aQIV group compared with the QIV group for each of the subgroups evaluated in the study. No notable differences in immunogenicity between aQIV and QIV for the rest of the influenza strains was observed, with the exception that a higher Day 22 immune response for aQIV regarding the A/H3N2 strain in the subgroup of subjects who had not received an influenza vaccination within the previous 3 influenza seasons, and for the A/H3N2 and B/Yamagata strains in the subgroup of subjects with a high

comorbidity risk score (≥50). However, it is unclear the relevance of these differences since for these two analyses, the GMT estimates determined for each of the subgroups had wide 95%CI and these CI overlap for the two subgroups analysed within the two analysis made (previous history of vaccination and comorbidity score).

To support the use of aQIV in this age group the applicant also provided data comparing the immune response of an aTIV vs a non-adjuvanted TIV, in subjects 50 to 64 yoa (trial V7P38), subjects 50 to 60 yoa (trial V70P3), and in the age group 18- 60 (Baldo et al, 2007) also pointed out in the direction of a higher immunity induced by the adjuvanted vaccine. In fact, consistently, in the three RCTs a higher immune response (in terms of GMTs), against all three viral components, was observed for the adjuvanted vaccine as compared to the non-adjuvanted one. It is noted that this increase in GMT was statistically significant [i.e., the upper limit of the 95%CI of the GMTR (TIV vs aTIV) was lower than 1] for the three strains in trial V70P3 and for two strains in trial V7P38 and in the study by Baldo et al).

Moreover, the applicant also provided results from three vaccine effectiveness studies: two retrospective cohort studies sponsored by Seqirus and one public health surveillance study carried out by the United Kingdom Health Security Agency (UKHSA) that also indicated adequate vaccine effectiveness of the MF59C.1 adjuvanted vaccine in the 50-64 and in the 65-74 years age group.

Collectively, and despite the limitations of some of these data, it is concluded that all evidence provided is sufficient to support approval, from the efficacy point of view, of the use of aQIV in the 50-64 years age group.

The evidence presented in these studies supported the idea of an increased effectiveness of aTIV vs non-adjuvanted vaccines in terms of reduction of influenza-related office visits among the elderly.

Concomitant administration (aTIV)

Data from publications regarding concomitant use of Fluad with PPSV23 and PCV13 was provided, but they were not complete CSRs and no conclusion could be made in the SmPC. To include coadministration data in the SmPC an assessment on the whole set of information regarding the clinical studies to support the decision to include those data in the PI would be needed. If the applicant wishes to reflect coadministration data in the SmPC, this should be done via variation with complete set of data.

Paediatric data

With regards to the paediatric data, efficacy, immunogenicity and safety of Fluad Tetra (aQIV) was evaluated in clinical study V118_05, a multi-centre, randomised, observer-blinded, controlled study conducted in the 2013-14 (season 1) and 2014-15 (season 2) Northern Hemisphere seasons in children of 6 months to less than 6 years. Children less than 3 years of age received 0.25 ml vaccine, older children received 0.5 ml vaccine. Over the two seasons covered in the study, the attack rate of (RT-PCR confirmed) influenza was similar in the aQIV group (4.9%) as compared to the comparator group (4.9%). 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 Efficacy Set population, 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]). As a result the primary objective of the study was not met. Therefore efficacy was not demonstrated. Consequently, these data are insufficient to conclude a positive B/R however the appropriate data are reflected in the SmPC which is appropriate.

2.5.7. Conclusions on the clinical efficacy

The CHMP concludes that clinical efficacy/immunogenicity data supports an indication for adults above

50 years of age.

Further, whilst no paediatric indication is requested, paediatric data are available and are included in section 5.1 of the SmPC which is appropriate.

2.5.8. Clinical safety

The clinical development programme to support registration of aQIV in individuals 65 years of age and above builds on aQIV study V118_20, phase III study V118_18, the aTIV study V70_27, aQIV V118_23, 12 supportive aTIV revaccination studies and the cumulative post-marketing experience with aTIV.

The 12 supportive studies include 5 supportive aTIV studies (Year 1: V7P3, V7P5, V7P7, V7P8 and V7P25) and 7 revaccination studies for 2 consecutive years (Year 2: V7P3X1, V7P5X1, V7P7X1, V7P8X1 and V7P25X1) or 3 consecutive years (Year 3: V7P3X2 and V7P5X2)

2.5.8.1. Patient exposure

The table below 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 5146 subjects were exposed aTIV (aTIV-1 and aTIV-2).

Table 56: Overall extent of exposure

Study	aQIV N = 4269	aTIV (aTIV-1) N = 4702	aTIV-2 N = 444	TIV N = 4038	Total 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

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. In studies V7P3, V7P5, V7P7, V7P8, V7P25, 1,214 subjects received Vaccination 1 (Year 1). From these, 822 were included in the respective extension studies (V7P3X1, V7P5X1, V7P7X1, V7P8X1, V7P25X1) for Year 2, and 237 of them received the third vaccination (Year 3: V7P3X2, V7P5X2).

Table 57: 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

Safety data used to support the use of aTIV in adults between 50 and 64 years of age is derived from study V118_23. The Overall Safety Set is the same as All Enrolled Set and it included 2043 participants, of these 1027 participants received aQIV and 1016 participants received QIV.

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 58: 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)

	aQIV N = 889	aTIV-1 N = 445	aTIV-2 N = 444	Total N = 1778
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

A 97.7% of 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 59: 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%)
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 60: 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)

	aTIV N = 3545	TIV N = 3537	Total N = 7082
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 the 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 Table 61.

Table 61: 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

2.5.8.2. 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 categorised 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 submitted the list of events considered AESIs for study V118_20, provided by the investigators, as requested by the co-rapporteur in the d120 LoQ.

An overview of AEs for studies V118_20, V118_18, and V70_27 is provided below in ***Table 62***.

Table 62: 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
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.

In study V118_23, the Solicited Safety Set included 2028 subjects (99.3% of Overall Safety Set), of which 1020 subjects received aQIV and 1008 subjects received QIV.

In the 7-day period after vaccination, the percentage of subjects reporting solicited AEs (any) was higher in the aQIV group than the QIV group (65.9% vs 53.7%). The percentage of subjects reporting solicited local AEs also tended to be higher in the aQIV group than the QIV group (49.8% vs 30.4%), while the percentages of subjects reporting solicited systemic AEs were similar between the two vaccine groups (45.3% vs 40.0%). The use of antipyretic/analgesics for treatment or prevention of pain/fever was similar between the aQIV and QIV groups (12.9% vs 9.6%).

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).

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.

The most commonly reported local solicited AEs were any injection site pain (aTIV, 25% 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%, sever fever (≥40ºC) 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.

Study V118_23

The most commonly reported solicited local AE in both vaccine groups was injection site pain, with a higher percentage of subjects reporting pain in the aQIV group compared with the QIV group (47.1% vs 28.1%). The percentages of subjects reporting induration in the aQIV and QIV groups were 7.9% and 3.5%, respectively and for erythema, 7.8% and 3.1%, respectively. The majority of solicited local AEs reported were mild or moderate in severity; severe solicited local AEs were reported by very few subjects (≤4 subjects per symptom) in either vaccine group.

In both aQIV and QIV groups, more subjects reported solicited local AEs during the Day 1-3 time interval (49.5% and 29.9%, respectively) than in the Day 4-7 time interval (9.3% and 5.9%), with onset most commonly reported on Day 1 or Day 2. In both vaccine groups, the majority of solicited local AEs were observed in ≤3 days.

There were few reports of solicited local AEs continuing or starting after Day 7. Injection site pain and erythema were reported after Day 7 by 4 of 1020 subjects (0.4%) and 2 of 1020 subjects (0.2%), respectively, in the aQIV group. In the QIV group, ecchymosis and injection site pain were reported by 2 of 1008 subjects (0.2%) and 1 of 1008 subjects (0.1%), respectively.

The percentage of subjects reporting individual solicited systemic AEs was generally similar between the two vaccine groups. The most frequently reported solicited systemic AEs in both the aQIV and QIV groups were fatigue (29.5% and 24.3%, respectively) and headache (22.2% and 20.4%). Myalgia was reported by 13.0% in the aQIV and 7.2% of subjects in QIV groups, and arthralgia was reported by 13.7% and 9.4% of subjects, respectively.

The majority of solicited systemic AEs were mild or moderate in severity, with low proportions of subjects reporting severe solicited systemic AEs (2.2% in both vaccine groups). The percentages of subjects reporting fever (≥38.0°C) were low in both the aQIV and QIV groups (2.5% and 1.7%), with severe fever (≥39.0°C) in only 8 subjects (0.8%) in the aQIV group and 4 subjects (0.4%) in the QIV group. Only 1 subject, in the aQIV group, reported a body temperature of ≥40.0°C.

In both aQIV and QIV groups, more subjects reported solicited systemic AEs in the Day 1-3 time interval (40.4% and 32.3%, respectively) than in the Day 4-7 time interval (21.0% and 22.4%), being most commonly reported on Day 1 or Day 2. In both vaccine groups, most of solicited systemic AEs were observed in ≤3 days.

In total, 35 of 1020 subjects (3.4%) in the aQIV group and 40 of 1008 subjects (4.0%) in the QIV group reported solicited systemic AEs ongoing after Day 7. The most commonly events were fatigue, headache, and arthralgia, reported by 1.5%, 1.5%, and 1.2% of subjects, respectively, in the aQIV group, and by 2.1%, 1.3%, and 1.3% of subjects, respectively, in the QIV group.

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 AEs (≥1%) by preferred term (PT) were influenza-like-illness (aQIV, 2% versus aTIV-1, 2.7% versus aTIV-2, 2.7%), 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 aQIV group, an unsolicited AE considered possibly related to treatment, which mostly included injection site bruising, injection site erythema (0.7%), injection site induration (0.5%), injection site pruritus (0.5%), fatigue (0.3%) arthralgia (0.3%), myalgia (0.2%) and headache (0.2%).

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).

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.

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%).

Study V118_23

A similar percentage of participants with unsolicited AEs in aQIV and QIV was observed (16.5% vs 16.9%, respectively). The majority of AEs were assessed as mild or moderate in severity in both vaccine groups; few subjects reported severe AEs (aQIV: 2 subjects [0.2%]; QIV: 7 subjects [0.7%]). The percentage of subjects with unsolicited AEs assessed by the Investigator as related to the study vaccine was low in both the aQIV (3.2%) and QIV (3.1%) groups.

In both vaccine groups, unsolicited AEs were most commonly categorised in the SOC of "Infections and infestations". Unsolicited AEs reported by >1% of subjects were nasopharyngitis (1.6%) and rhinitis (1.5%) in the aQIV group and headache (1.3%) and rhinitis (1.1%) in the QIV group.

In both vaccine groups, related unsolicited AEs were most commonly categorised in the SOC of "General disorders and administration site conditions". The most common related unsolicited AEs were injection site pain (0.3%) and lymphadenopathy (0.3%) in the aQIV group and vertigo (0.3%) in the QIV group. Most related unsolicited AEs was observed in only 1 subject in each vaccine group.

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 hospitalisation 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.

2.5.8.3. 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, the second had an unknown onset day. 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. In both cases the investigators concluded 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

In study V70_27, 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).

Study V118_23

Deaths

There was 1 death reported during the study in the aQIV group, due to an AE of lung adenocarcinoma, assessed as not related to the study vaccine.

Other serious adverse events

From Day 1 through Day 271, SAEs were reported by 31 participants (3.0%) in the aQIV group and 31 participants (3.1%) in the QIV group. Most SAEs were reported by SOC of "Infections and infestations" (6 subjects in aQIV group and 7 subjects in QIV group) followed by "Cardiac disorders" (5 subjects in each group) and "Neoplasms benign, malignant and unspecified" (5 subjects in each group).

There were no related SAEs in the aQIV group.

One SAE of hypertensive crisis (for which the subject was hospitalised) that started on the day of vaccination in a subject in the QIV group was assessed by the Investigator as related to the study vaccine. However, the Sponsor assessed this event as not related to the study vaccine, because the subject's concurrent conditions of obesity, coronary sclerosis, hypercholesterolemia, and migraine provided alternative aetiology of the reported event.

Adverse events of special interest

From Day 1 through Day 271, 2 AESIs were reported by 2 subjects (0.2%) in the aQIV and no AESIs were reported in the QIV group.

One subject reported worsening of rheumatoid arthritis and one subject reported autoimmune thyroiditis. Both AESIs were assessed as moderate in severity and were assessed by both the Investigator and Sponsor as not related to the study vaccine. It should be noted that the subject reporting worsening of rheumatoid arthritis had a history of rheumatoid arthritis (since 2002) and therefore should have been excluded from participation in the V118_23 study (Exclusion Criterion #4).

2.5.8.4. Laboratory findings

Study V118_20, V118_18 and V118_23 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.

2.5.8.5. Safety in special populations

Intrinsic factor

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.

In study V118_23, the safety assessment by age cohort was performed in two age groups: 50 to ≤59 years and 60 to ≤64 years.

As observed for the overall study population, solicited local AEs were reported more frequently by subjects in the aQIV group than the QIV group for both subgroups (50 to 59 years: 53.2% vs 36.4%;

60 to 64 years: 44.8% vs 21.8%, respectively) and no difference in the percentage of solicited systemic AEs (50 to 59 years: 50.6% vs 43.5%; 60 to 64 years: 37.6% vs 35.0%)

In addition, in both vaccine groups, solicited local and systemic AEs were reported more frequently by subjects in the 50 to 59 years age subgroup than those in the 60 to 64 years age subgroup.

Regarding unsolicited AEs, no notable differences in the frequency in the 50 to 59 years age subgroup as in the 60 to 64 years age subgroup (aQIV: 16.9% vs 15.8%; QIV: 18.3% vs 15.0%).

Sex

In study V118_20, females reported more AEs than males (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 slight 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%).

In study V118_23, as observed for the overall study population, solicited local AEs were reported more frequently by subjects in the aQIV group than the QIV group for both subgroups (male: 40.0% vs 21.2%; female: 55.9% vs 36.3%, respectively) and there was no difference in the percentage of solicited systemic AEs (male: 39.0% vs 31.7%; female: 49.2% vs 45.3%) or unsolicited AEs (male: 13.8% vs 16.6%; female: 18.1% vs 17.1%)

In addition, in both vaccine groups, solicited local and systemic AEs were reported more frequently by subjects in the female subgroup than the male subgroup. No difference of incidence of unsolicited AEs by sex was observed.

By race

In study V118_23, the safety assessment by race cohort was performed in two race subgroups: Black or African American (69 subjects) and White (1946 participants). The small number of Black or African American subjects in these analyses limits any conclusion for these observations.

As observed for the overall study population, solicited local AEs were reported more frequently by subjects in the aQIV group than the QIV group in both subgroups (Black or African American: 52.8% vs 21.2%; White: 49.6% vs 30.7%) and no notable differences in the percentage of solicited systemic AEs (Black or African American subgroup: 61.1% vs 63.6%; White: 44.6% vs 39.4%) or unsolicited AEs (Black or African American subgroup: 5.1% vs 8.3%; White: 17.0% vs 17.3%).

In the aQIV group, no notable differences in the percentage of solicited local AEs by race were observed. However, there were higher frequencies of solicited systemic AEs and lower frequencies of unsolicited AEs in Black or African American subjects than in White. In QIV group, there were higher solicited local AEs and unsolicited AEs and lower solicited systemic AEs in White subjects than in Black or African American subjects.

By ethnicity

In study V118_23, the safety assessment by ethnicity cohort was performed in two ethnicity subgroups: Hispanic or Latino (25 subjects) and Not Hispanic or Latino (2000 participants). The small number of Hispanic or Latino subjects in these analyses limits any conclusion for these observations.

As observed for the overall study population, solicited local AEs were reported more frequently by subjects in the aQIV group than in the QIV group for the Hispanic or Latino ethnicity subgroup (57.1% vs 45.5%) and for the "Not Hispanic or Latino" ethnicity subgroup (49.7% vs 30.2%). No notable difference in the percentage of solicited systemic AEs was observed between the aQIV and QIV groups

for the "Not Hispanic or Latino" ethnicity subgroup (45.0% vs 39.8%), whereas a higher percentage of solicited systemic AEs in the Hispanic or Latino ethnicity subgroup in the aQIV group compared with the QIV group (64.3% vs 45.5%) was reported. In addition, no notable differences in the percentages of unsolicited AEs were observed (Hispanic or Latino ethnicity: 21.4% vs 25.0%; Not Hispanic or Latino: 16.4% vs 16.9%).

In aQIV groups, solicited local and systemic AEs and unsolicited AEs were reported more frequently by subjects of Hispanic or Latino ethnicity compared with subjects of "Not Hispanic or Latino". In QIV group, solicited local AEs and unsolicited AEs were reported more frequently by subjects of Hispanic or Latino ethnicity compared with subjects of "Not Hispanic or Latino" and no difference was observed regarding solicited systemic AEs.

By Comorbidity Risk Score

In study V118_23, as observed for the overall study population, solicited local AEs were reported more frequently by subjects in the aQIV group than the QIV group both subgroup (comorbidity risk score <50: 49.7% vs 30.3%; comorbidity risk score ≥50: 50.4% vs 31.3%) and there were no notable differences in the percentages of solicited systemic AEs (comorbidity risk score <50: 45.9% vs 39.4%; comorbidity risk score ≥50: 40.9% vs 45.8%) or unsolicited AEs (comorbidity risk score <50: 15.6% vs 17.1%; comorbidity risk score ≥50: 23.5% vs 15.3%)

For both vaccine groups, the percentages of subjects reporting solicited local and systemic AEs were similar between subjects with a comorbidity risk score <50 and subjects with a comorbidity risk score ≥50. Regarding unsolicited AEs in aQIV, higher incidence was observed in participants at risk, but this difference was not observed in QIV group.

Extrinsic factors

Country

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.

By Previous Vaccination History

In study V118_23, the safety assessment by Previous Vaccination History was performed in participants who had received an influenza vaccination in the previous 3 influenza seasons (subgroup YES) and in participants who had not received an influenza vaccination in the previous 3 influenza seasons (subgroup NO).

As observed for the overall study population, solicited local AEs were reported more frequently by subjects in the aQIV group than the QIV group for both subgroups (YES: 54.0% vs 35.0%; NO 44.3% vs 23.8%; N=438 and 416) and no notable differences in the percentage of solicited systemic AEs (YES: 48.5% vs 42.1%; NO: 41.1% vs 37.0%) or unsolicited AEs (YES: 16.2% vs 14.4%; NO: 16.8% vs 20.6%) were observed between the aQIV and QIV groups for both subgroup

For both vaccine groups, higher percentage of solicited local AEs was reported by subjects who had received an influenza vaccination in the previous 3 influenza seasons compared with subjects who had not and there was no difference in percentages of solicited systemic AEs or unsolicited AEs between subjects who had received an influenza vaccination in the previous 3 influenza seasons and subjects who had not.

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). Most of these withdrawals occurred because of death not related to the vaccine (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 from the study.

In study V118_23, one subject in the QIV group reported an AE leading to withdrawal from the study: severe aphasia, which was assessed as not related to the study vaccine.

2.5.8.6. Post marketing experience

aTIV was first licensed for use in persons 65 years of age and older in Italy in 1997.

The cumulative reporting period for the post marketing analysis presented in this submission for aTIV is from the International Birth Date (IBD) of 15 May 1997 until the DLP of the most recent PSUR (15 Mar 2024). Cumulatively, over 195 million doses of aTIV were distributed, and 6,982 spontaneous aTIV-confirmed individual case safety reports (ICSRs) were received. The analysis of the cumulative post-marketing aTIV safety data confirms that the safety profile of aTIV remains consistent with the safety profile established in clinical studies, and no new safety concerns have been identified in any age group.

In addition to the information related to aTIV, the cumulative reporting period for the post marketing analysis for aQIV is presented in this submission, from the IBD of 24 Sep 2019 until 15 Mar 2024 (DLP of the most recent PSUR). Cumulatively, over 143 million doses of aQIV were distributed, and 6,962 spontaneous aQIV-confirmed individual case safety reports (ICSRs) were received. The analysis of the cumulative post-marketing aQIV safety data confirms that the safety profile of aQIV remains consistent with the safety profile established in clinical studies, and no new safety concerns have been identified in any age group.

2.5.9. Discussion on clinical safety

The safety assessment of aTIV was based on the data generated during the development of aQIV (Fluad Tetra), specifically during the MAA (EMEA/H/C/004993) which included the approval for adults above 65 years of age, during the extension of indication variation (EMEA/H/C/004993/II/0043) to include adults above 50 years of age and on the cumulative post-marketing data with aTIV and aQIV.

Data for aQIV are relevant to aTIV because both vaccines are manufactured using the same process and have overlapping compositions. The warnings, recommendations and contraindications that currently apply to aQIV do also apply to aTIV.

The overall safety database for aTIV was mainly derived from the pivotal aQIV study (V118_20), the pivotal aTIV study (V70_27), the study V118_18, the supportive aTIV revaccination studies and the study V118_23 regarding the extension of indication of aQIV.

After the review of the submitted data collected in the pivotal aTIV study (V70_27), the aTIV vaccine was well tolerated in subject aged ≥65 years. The incidence of solicited local and systemic AEs was higher in aTIV compared to TIV but this is not considered as a relevant safety issue. The majority of adverse events was mild or moderate in severity and resolved in few days. No difference was observed regarding unsolicited AEs. The incidence of SAEs and NOCDs was low in both groups. There was one

SAE judged by the investigator as possibly related to aTIV, namely as a case of bronchitis with onset 8 days after the administration of the study vaccine.

According to the data submitted in the aQIV study (V118_20) and other supportive studies no new safety concern was identified.

In study V118_18, the reactogenicity profiles of the aQIV and Boostrix vaccines were generally comparable. The observed rates of solicited local AEs were higher in the aQIV group compared to the Boostrix groups. No increase in the frequency of severe solicited AEs was observed following aQIV administration. The percentage of subjects reporting unsolicited AEs, including those assessed as possibly related to vaccination were comparable across study groups. Overall, no safety concerns were observed.

It can be concluded that the safety profile of aQIV and aTIV was comparable in subjects aged ≥65 years.

Accordingly, it is expected that the safety profile of aTIV in individuals aged 50-64 years would be similar to the safety profile observed in the study V118_23 with aQIV vaccine in this cohort. It is anticipated that the vaccine aTIV would be well tolerated in subjects aged 50-64 years with good reactogenicity and safety profile. In addition, it is also expected that the reactogenicity of the aTIV in subjects aged 50-64 years would be higher than in subjects older than 65 yoa, in the same line that was observed with aQIV in the study V118_23, but this is not considered as a relevant safety issue.

Since aTIV was first licensed in 1997, over 195 million doses of aTIV have been distributed, and since aQIV was authorised, over 143 million doses of aQIV have been distributed. The analysis of the cumulative post marketing safety data for aTIV and aQIV confirms that the safety profile of the two vaccines remains consistent with the safety profile established in clinical studies, and no new safety concerns have been identified in any age group for any of the vaccines.

Therefore, the safety profile of aTIV will be considered to be adequate to support the indication for prophylaxis of influenza in subjects ≥50 years of age.

2.5.10. Conclusions on the clinical safety

The CHMP concludes that clinical safety data supports an indication for adults above 50 years of age.

2.6. Risk Management Plan

2.6.1. Safety concerns

None

2.6.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Additional pharmacovigilance activities recommended under EMA guidelines				
DRIVE analysis - A non-interventional study of vaccine effectiveness in the EU; seasonal influenza vaccine (aTIV/aQIV) versus no vaccination in elderly ≥ 65 years (DRIVE analysis).	To perform an analysis of influenza vaccine effectiveness of aTIV/aQIV vaccination versus no vaccination in elderly ≥ 65 years	Measure of vaccine effectiveness in routine care.	Planned for the initial influenza season of launch and annually thereafter.	Annual submission of results planned in December

2.6.3. Risk minimisation measures

None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 3.1 is acceptable.

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

- applicant is requested to reflect in the relevant sections the waiver regarding the requirement to submit enhanced safety surveillance data for all seasonal influenza vaccines as agreed by PRAC.
- Considering that DRIVE is not addressing a safety concern in the RMP and relates to effectiveness, the project should be removed as an additional pharmacovigilance activity in the RMP. However, the applicant is expected to provide regular updates and results on the project in PSURs.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

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

CSL Seqirus completed a consultation with target patient groups (user testing) on the Fluad Tetra (QIV) Package Leaflet (PL) and submitted the results (final report dated, 15 July 2019), as part of the initial EU marketing authorisation application (MAA) that was approved on 20 May 2020. As noted in the Europe Public Assessment Report (EPAR) from the original authorisation, the results of the user consultation with target patient groups met the criteria for readability as described in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Influenza is a highly contagious infectious disease that occurs in epidemics throughout the winter months in temperate climates in the Northern and Southern Hemispheres. The influenza virus is an orthomyxovirus with two clinically relevant types (types A and B).

Influenza is characterised by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis (Temte and Prunuske 2010) and generally resolves within 2 to 7 days. However, influenza can exacerbate underlying medical conditions and/or lead to secondary viral or bacterial pneumonia for some people, notably older adults and those with chronic diseases (including pulmonary or circulatory disorders, metabolic disorders such as diabetes mellitus, renal dysfunction, or immunosuppression) (Rothberg et al. 2008; Fiore et al.2009).

3.1.2. Available therapies

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 strategy to lower the burden of influenza disease. However, the efficacy of influenza vaccines in older individuals is significantly lower than in younger individuals due to the aging of the immune system as well as underlying medical conditions, factors which increase the risk of influenza complications and interfere with immune responses.

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

Vaccines against seasonal influenza may need to be updated in composition on a yearly basis to include the latest circulating viruses and people need to get vaccinated accordingly. The protection afforded by conventional influenza vaccines is driven by how well the strains in the vaccine match the viruses that circulate during influenza season (antigenic match).

3.1.3. Main clinical studies

The clinical development programme to support the authorisation of aTIV in individuals ≥50 years of age is based on the results of the pivotal aTIV immunogenicity and safety study V70_27, aQIV immunogenicity and safety study V118_20, aQIV efficacy and safety study V118_18 and aQIV immunogenicity and safety study V_118_23. 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 post-marketing data.

V70_27 was 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, individual 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).

V118_20 was 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.

V118_18 was a randomised, observer-blind, controlled, multicentre study to evaluate the efficacy, safety and immunogenicity of aQIV compared to non-influenza Vaccine comparator in adults ≥65 years of age.

V118_23 was a randomised, comparator-controlled, observer-blind, multicentre study to evaluate the immunogenicity and safety of aQIV versus a licensed non-adjuvanted QIV comparator (QIV) in individuals 50 to 64 years of age. The non-inferiority and superiority of the immune response of aQIV compared with QIV were evaluated in a sequential manner. Immunogenicity, antibody persistence, reactogenicity, and safety of the two vaccines were also assessed in this study population.

3.2. Favourable effects

In study V70_27, non-inferiority was demonstrated for GMT ratios and SCR differences for all 3 strains in individuals 65 years of age and older. The immune response of aTIV was consistently higher as compared to the response to the authorised non-adjuvanted trivalent vaccine (TIV).

In study V118_20, the primary immunogenicity 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 SCR in individuals 65 years of age and older.

In study V118_23, the primary endpoint aimed at demonstrating non-inferiority of aQIV compared with a non-adjuvanted QIV was successfully demonstrated in this study population of individuals 50 to 64 years of age. In relation to the other primary endpoint regarding superiority, the first analysis of the HI data showed superior immune response of aQIV versus QIV for only 1 of the 4 vaccine strains (A/H1N1 [UL of the 95% CI for Day 22 GMTr: 0.87) and thus the prespecified success criteria for meeting this primary endpoint was not met since it required showing superiority for at least two viral strains. An additional post-hoc analysis, based on a "complete serology set" which incorporated additional serum samples, showed superior immune response of aQIV versus QIV for 2 of the 4 vaccine strains (A/H1N1 [UL of the 95% CI for Day 22 GMTr: 0.88] and A/H3N2 [UL of the 95% CI for Day 22 GMTr: 0.998]).

Persistence of the antibody responses to each of the 4 vaccine strains was observed 6 months after vaccination (Day 181) in both vaccine groups, with evidence for a higher immune response to the A/H1N1 strain (UL of the 95% CI for Day 181 GMTr: 0.94) in the aQIV group compared with the QIV group.

Subgroup analyses identified a higher Day 22 immune response for aQIV versus QIV for multiple vaccine strains in clinically meaningful subgroups. For individuals with a higher probability of hospitalisation due to pneumonia, influenza or death as defined by a comorbidity risk score ≥50, higher antibody responses were observed for A/H1N1, A/H3N2 and B/Yamagata strains. In addition, for persons without a history of influenza vaccination within the previous 3 years, higher responses were observed for A/H1N1 and A/H3N2 strains.

Supportive randomised control trials compared the immune response of an MF59C.1 adjuvanted trivalent influenza vaccine vs a non-adjuvanted one, and the results indicate overall a higher immune response of the MF59C.1 adjuvanted vaccines compared to the non-adjuvanted ones in the age group 50 to 64 years of age.

Data on vaccine effectiveness comparing aTIV vs QIV for the prevention of influenza-related medical encounters significantly favoured aTIV in the overall study population (≥65 years of age). The aTIV also demonstrated a higher or comparable clinical effectiveness to a high dose TIV in the 3 influenza seasons.

3.3. Uncertainties and limitations about favourable effects

Although the haemagglutinin inhibition (HI) response was higher in individuals 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.

There are no data in elderly with a compromised immune system, and little to no data in the frail elderly.

In study V118_18, 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 was not satisfied. Similarly, none of the four secondary efficacy objectives were met. Therefore, this study could not support to the demonstration of efficacy in the ≥65 age group.

Regarding the results for the 50 to 64 years of age group, demonstration of non-inferiority of aQIV vs QIV was clearly demonstrated in terms of SCR differences and GMT titres for all four viral strains.

However, this apparent increase in the immune response provided by the adjuvanted vaccines did only translate, in the first immunogenicity analysis, in showing superiority against one viral strain (H1N1), and in the post-hoc analysis it is noted that the results for A/H3N2 strain marginally exceeded the predefined criterion.

A post-hoc analysis, which incorporated additional serum samples, showed superior immune response of aQIV versus QIV for 2 of the 4 vaccine strains (A/H1N1 and A/H3N2), and thus met the specified success criteria for this primary endpoint. From a methodological and statistical point of view, this post-hoc sensitivity analysis can never replace or rescue the main analysis, as there is no free alpha for confirmatory testing.

It is noted that results from trial V118_23 covered only one influenza season, and therefore it is unknown whether these can be extrapolated to other seasons, since the composition of vaccine is updated annually.

The results from the subgroup analyses that showed higher antibody responses for individuals at higher risk of influenza complications due to baseline comorbidities and for individuals without a history of influenza vaccination within the previous 3 years, need to be taken with caution since for both cases the differences found were not statistically significant.

3.4. Unfavourable effects

The safety assessment of aTIV was based in the data generated during the development of aQIV, mainly during the MA (EMEA/H/C/004993/0000) and during the extension of indication variation (number procedure EMEA/H/C/004993/II/0043).

In individuals aged ≥65 years, the incidence of solicited local and systemic AEs was higher in aTIV compared to the non-adjuvanted vaccine. The most common solicited AEs were injection site pain, tenderness, myalgia, fatigue and headache. In the same line, the percentage of individuals who reported at least one solicited AE after aQIV vaccination was higher than the comparator.

In individuals aged 50-64 years, the safety was evaluated with aQIV in the clinical trial V118_23. A higher percentage of individuals reported reactogenicity in the aQIV group as compared with the nonadjuvanted QIV group. The most comment solicited AEs were injection site pain, fatigue and headache.

The majority of solicited AEs (local and systemic) with aTIV or aQIV in individuals above 50 years of age were mild or moderate in severity and were resolved in few days.

Moreover, the analysis of the cumulative post-marketing aTIV and aQIV safety data confirms that the safety profile of both vaccines remains consistent with the safety profile established in clinical studies, and no new safety concerns have been identified in any age group with any vaccine.

3.5. Uncertainties and limitations about unfavourable effects

There were no data with aTIV in individuals aged 50-64 years. However, aQIV was well tolerated, showing a good reactogenicity and safety profile in individuals aged 50-64 years. Therefore, it would be expected that aTIV will have a similar safety profile than aQIV in this age group.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The immunogenicity of Fluad (trivalent formulation) is relevant to Fluad Tetra (quadrivalent formulation) 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. Studies submitted 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) (EMA/CHMP/VWP/457259/2014) 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.

In the 50 to 64 years of age group, non-inferiority of aQIV vs QIV in terms of SCR differences and GMT titres was demonstrated for the four influenza viral strains. Superiority on aQIV in terms of GMT for at least 2 of the influenza viral strains was not met. An additional post-hoc analysis showed superior immune response of aQIV versus QIV for 2 of the 4 vaccine strains (A/H1N1 and A/H3N2), however this is of exploratory nature.

Data from three RCTs comparing the immune response of an MF59C.1 adjuvanted trivalent influenza vaccine vs a non-adjuvanted one, indicated overall a higher immune response of the MF59C.1 adjuvanted vaccines compared to the non-adjuvanted ones in the age group 50 to 64 years of age. Moreover, evidence from retrospective cohort studies and public health surveillance also indicate adequate vaccine effectiveness of the MF59C.1 adjuvanted vaccine in the adults from 50 years of age.

In conclusion, taking into account the variability of the immune response to influenza vaccines, and in the absence of a clear-cut criterion to demonstrate superiority of an adjuvanted vs a non-adjuvanted vaccine (according to the current CHMP guideline on influenza vaccines), it is considered that collectively the efficacy evidence provided is sufficient to support use of aTIV in the 50-64 years age group.

Regarding safety, the aQIV vaccine is well tolerated in individuals aged 50-64 years. The only clear difference in the safety profile of aQIV and QIV relates to the higher frequency of site injection pain and this is not considered a relevant safety issue.

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/comparator, within limits of what can be expected for influenza vaccines, the benefit-risk balance can be considered positive.

3.6.2. Balance of benefits and risks

As an immunological advantage of the adjuvant has been demonstrated and accepted in comparison to a non-adjuvanted influenza and as the reactogenicity observed in clinical trials is, albeit increased

compared with 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 benefit-risk balance of Fluad is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

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

Prophylaxis of influenza in adults 50 years of age and older.

Fluad should be used in accordance with official recommendations.

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

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

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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