EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 November 2023
EMA/533902/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Fluad Tetra

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

Procedure No. EMEA/H/C/004993/II/0043

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

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List of abbreviations

ACIP Advisory Committee on Immunization Practices
AE adverse event
AESI adverse event of special interest
aQIV MF59-adjuvated Quadrivalent Influenza Vaccine
aTIV MF59-adjuvanted Trivalent Influenza Vaccine
CBER Center for Biologics Evaluation and Research
CDC Centers for Disease Control and Prevention
CHMP Committee for Medicinal Products for Human Use
CI confidence interval
CRO Contract Research Organization
CSR Clinical Study Report
CTAB cetyltrimethylammonium bromide
DMC Data Monitoring Committee
EC Ethics Committee
EDC electronic data capture
eCRF electronic Case Report Form
EMA European Medicines Agency
FAS Full Analysis Set
FDA United States Food and Drug Administration
GCP Good Clinical Practice
GDPR General Data Protection Regulation
GMFI geometric mean fold increase
GMT geometric mean titer
GMTr geometric mean titer ratio
HA hemagglutinin
HI hemagglutination inhibition
ICH The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IB Investigator’s Brochure
ICF informed consent form
ID identification
IRB Institutional Review Board
IRT Interactive Response Technology
MF59 MF59C.1 adjuvant
NH Northern Hemisphere
PFS pre-filled syringe
PPS Per Protocol Set
PVRM Pharmacovigilance and Risk Management
QIV Quadrivalent Influenza Vaccine
SAE serious adverse event
SAP Statistical Analysis Plan
SDA Source Document Agreement
SH Southern Hemisphere
SOC System Organ Class
SOP Standard Operating Procedure
SUSAR Suspected Unexpected Serious Adverse Reaction
TIV Trivalent Influenza Vaccine
UL upper limit
UK United Kingdom
US United States
WHO World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Seqirus Netherlands B.V. submitted to the European Medicines Agency on 3 April 2023 an application for a variation.

The following variation was requested:

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

Extension of indication to include adults 50 years of age and older for Fluad Tetra, based on final results from study V118_23; this is a phase 3, randomized, observer-blind, controlled, multicenter, 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. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. Version 2.9 of the RMP has also been submitted. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0355/2020 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Sol Ruiz.

Timetable	Actual dates
Submission date	3 April 2023
Start of procedure:	22 April 2023
CHMP Rapporteur Assessment Report	14 June 2023
PRAC Rapporteur Assessment Report	23 June 2023
PRAC Outcome	6 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 July 2023
Request for supplementary information (RSI)	20 July 2023
CHMP Rapporteur Assessment Report	4 October 2023
PRAC Rapporteur Assessment Report	13 October 2023
PRAC Outcome	26 October 2023
CHMP members comments	27 October 2023
Updated CHMP Rapporteur Assessment Report	31 October 2023
Opinion	9 November 2023

2. Scientific discussion

2.1. Introduction

Adjuvanted Quadrivalent Influenza Vaccine (aQIV; Fluad Tetra/Quad/Quadrivalent) is an egg-derived inactivated subunit quadrivalent influenza virus vaccine adjuvanted with MF59C.1 (MF59), a squalene-based oil-in-water emulsion. Fluad Tetra/Quad/Quadrivalent is licensed in the European Union [EU] for use in adults aged 65 years and over.

Seqirus submits a Type II variation for the extension of the age indication for Fluad Tetra, for use in persons 50 years of age and older, based on final results from study V118_23 (EudraCT: 2021-001721-40). This is a Phase 3, Randomized, Observer-blind, Controlled, Multicenter, 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.

2.1.1. Problem statement

To assess the registration of aQIV for use in persons 50 years of age and older, this assessment report provides a summary of the benefits and risks of aQIV for prevention of influenza in persons 50 to 64 years of age based on the data generated in clinical study V118_23.

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).

Type A viruses are associated with both annual epidemics and pandemics, and B viruses contribute to annual epidemics. The type A viruses are further divided into different subtypes, of which the A/H3N2 and A/H1N1 viruses are the most clinically relevant for 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.

Influenza is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis 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).

State the claimed the therapeutic indication

The MAH submitted a Type II variation for the extension of the age indication for Fluad Tetra. The proposed indication reads "Prophylaxis of influenza in adults (50 years of age and older). Fluad Tetra should be used in accordance with official recommendations."

Epidemiology, risk factors and prevention of influenza disease

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.

For adults over the age of 50 years, the ability to respond well to vaccination is affected by immunosenescence, in which advancing age diminishes the effectiveness of the immune system. Immune responses against conventional trivalent influenza vaccines in adults ≥58 years of age have been shown to be 10% to 23% lower than in adults younger than 58 years of age.

While it is well established that adults 65 years and older are at greater risk of serious complications from influenza compared with young, healthy adults, there is growing recognition of a high burden of disease in adults aged 50 to 64 years of age.

In the EU, approximately 93 million people are between the age of 50 to 64 years. The impact of seasonal influenza on hospitalizations 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 hospitalizations, 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%. For deaths, the percentage of all-cause mortality caused by influenza activity in the 50 to 64 years age group was between 1.7% and 3.4%, lower than the 3.2% and 7.4% range observed in the age group 65 years and older. 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. These data indicate influenza disease contributes to a substantial health burden in the 50 to 64-year-old population.

In the EU, seasonal influenza vaccine is also recommended for older adults with age of recommendation ranging from ≥50 to ≥65 years.

Given increased susceptibility to infectious diseases with aging, novel vaccine formulations are needed to elicit effective immunity in older individuals. One way to increase the immunogenicity of influenza vaccines is by using adjuvants. The mechanism of action of the adjuvant MF59 has been extensively detailed in the initial dossier. The immune-enhancing benefit of the adjuvant MF59 in aQIV has been demonstrated in persons 65 years of age and older and its effect is described for persons 50 years and older in the current procedure.

2.1.2. About the product

The investigational product in this study, adjuvanted quadrivalent influenza vaccine (aQIV), is an MF59-adjuvanted egg-derived subunit inactivated quadrivalent influenza virus vaccine. A 0.5-mL dose has been formulated to contain 15 µg hemagglutinin (HA) of each influenza virus strain, including both A/H1N1 and A/H3N2 strains and strains of both B lineages.

Adjuvanted Quadrivalent Influenza Vaccine (aQIV; Fluad Tetra/Quad/Quadrivalent) is an egg-derived inactivated subunit quadrivalent influenza virus vaccine adjuvanted with MF59C.1 (MF59), a squalene-based oil-in-water emulsion. The quadrivalent version of Fluad, containing A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains, is licensed in Australia (since 24 Sep 2019), the US (since 21 Feb 2020), the European Union plus Iceland, Norway and Liechtenstein (since 20 May 2020), New Zealand (since 17 Dec 2020), United Kingdom (since 01 Jan 2021), Argentina (since 27 May 2022), Brazil (since 26 September 2022), Republic of Korea (since 19 September 2022) and Taiwan (since 07 February 2023) for use in adults aged 65 years and older.

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

The clinical development program to support registration of the quadrivalent version of Fluad (adjuvanted quadrivalent influenza vaccine; aQIV) builds upon the development program of the trivalent version of the vaccine (aTIV). The trivalent version (containing 2 influenza A strains [A/H1N1 and A/H3N2] and 1 influenza B strain [B/Yamagata or B/Victoria]) has been licensed for use in persons 65 years of age and older in Europe since 1997 and in the US since 2015.

Study V118_23 was designed as a randomized, comparator-controlled, observer-blind, multicenter study to evaluate the immunogenicity and safety of aQIV with respect to a licensed nonadjuvanted QIV comparator in subjects 50 to 64 years of age.

The design of the study is consistent with the EMA Guideline on Influenza Vaccines (EMA 2016) and with the CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (CBER 2007).

The Statistical Analysis Plan (SAP) for Study V118_23 is compliant with International Conference on Harmonization (ICH) Harmonized Tripartite Guideline, 5 February 1998, Statistical Principles for Clinical Trials, E9; World Health Organization, WHO Technical Report, Series No. 924. 2004, Annex 1: Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations; and FDA Center for Biologics Evaluation and Research (CBER) Guidance for Industry, May 2007, Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines.

Fluad Tetra (aQIV) is authorised in the EU, from May 2020, for subjects older than 65 years of age and older. This quadrivalent influenza vaccine contains 15 µg hemagglutinin (HA) of each influenza virus strain, including both A/H1N1 and A/H3N2 strains and strains of both B lineages. The vaccine is an egg-derived,

inactivated, MF-59-adjuvanted vaccine that shows an increased immunogenicity in subjects 65 YOA and older.

Considering the public health impact of severe disease caused by influenza infection in the age group 50-64 YOA (particularly in those with certain comorbidities), it is acknowledged that the MAH decided to carry out study V118_23 to assess the benefits and risks of this adjuvanted vaccine in this age group, in order to support registration of aQIV for use in persons from 50 years of age.

2.1.4. General comments on compliance with GCP

Study V118_23 was designed, implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH E6(R2)), with applicable local regulations including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare, with Seqirus codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Parliament 2001; FDA 1997; ICH 2016).

The clinical trial V118_23 was performed in accordance with GCP, as indicated by the MAH.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

Due to the nature of the product (i.e. a vaccine comprised of proteins in an adjuvanted buffer solution) no ERA studies have been performed, since the product is unlikely to result in a significant risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

The absence of ERA studies is considered acceptable due to the nature of the product.

Considering the above data, aQIV is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The initial aQIV regulatory submission included immunogenicity, efficacy, and safety data of 4 completed paediatric aQIV studies (V104P2, V118_05, V118_05E1, and V118_05E3), 2 completed older adult aQIV studies (≥65 years of age; V118_18 and V118_20) and several aTIV studies conducted in paediatric and adult populations (see Clinical Overview – Paediatric and Clinical Overview – Elderly, respectively).

The current data package includes data from Study V118_23 which compared immunogenicity and safety of aQIV vs a licensed non-adjuvanted QIV comparator in subjects 50 to 64 years of age.

2.3.2. Clinical pharmacology

Overview of Biopharmaceutics

No bioequivalence studies were performed in the aQIV clinical development program.

No changes have been made to the formulation of aQIV for the requested extension of the age indication: the formulation is identical to the approved marketed formulation in adults 65 years of age and older.

Overview of Clinical Pharmacology

No classical clinical pharmacology or pharmacokinetic studies were performed in the development program of aQIV and aTIV. Pharmacokinetic properties of influenza vaccines do not provide useful information for establishing adequate dosing recommendations (EMA 2006).

2.3.3. Assays supporting immunogenicity assessment

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). Serological samples were collected at baseline (ie, before vaccination) and at 21 days after vaccination for evaluation of immunogenicity.

All sera were tested by validated hemagglutination inhibition (HI) assays performed at one central laboratory (Viroclinics Biosciences BV, Rotterdam, The Netherlands).

The hemagglutination-inhibition (HAI) assay is a method for assessing immune responses to influenza virus hemagglutinin (HA), a protein on the surface of a virus particle. This protein can agglutinate erythrocytes by binding to receptors on the membrane of red blood cells. Specific attachment of antibody to the antigenic sites on the HA molecule interferes with the binding between the viral HA and receptors on the erythrocytes. This results in an inhibition of the agglutination. The highest dilution of antibody, which still prevents agglutination of the virus with erythrocytes, can be used to quantitate virus specific antibodies. In addition, the HAI assay can be used for the typing and subtyping of seasonal strains of influenza viruses by using reference sera, for instance obtained from ferrets after infection with selected influenza virus strains.

A validation report of the hemagglutination inhibition assay for the following influenza strains is provided (VC-VAL-VAL150-RPT_C): 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 in SOP VC-M005) 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.

The use of the Hemagglutination Inhibition (HI) assay as the primary assay to assess vaccine immunogenicity is in agreement with the recommendations of the Guideline on Influenza Vaccines (Non-clinical and clinical module) (EMA/CHMP/VWP/457259/2014). It is also considered adequate that serum samples were analysed for HI titres both at baseline (before vaccination) and at day 21 post-vaccination.

The MAH provided a detailed document describing the validation of the HI assay for the four viral antigens, which included assessing the precision, repeatability, intermediate precision, format variability, dilution

linearity/relative accuracy, and specificity of the HI test. The data submitted supported the adequate validation of the HI assay. The MAH also provided the protocol.

Considering the results described below, it was considered important for this application that the microneutralization (MN) data were made available during the procedure since these data may give further insight into the effect of the adjuvanted vs. control vaccine. The MAH indicated that using MN assays was an exploratory objective and that neutralization testing is currently not planned to be conducted. Indeed, these data would have been valuable in assessing this variation procedure in a situation in which the superiority criterion based on HI titres was not met. Nonetheless, following assessment of the new data provided by the MAH in response to the MO, the data based on neutralization assays was not considered critical, and thus this issue was not further pursued.

2.4. Clinical efficacy

2.4.1. Dose response study

The vaccine tested in trial V118_23 contains the influenza hemagglutinin (HA) antigen from four viral strains grown in eggs, and the adjuvant MF-59. The dose (0.5 ml) of 15 µg HA per viral strain is in agreement with the Eur. Ph. requirements. This same composition is the one currently approved for use in subjects 65 years of age and older and it is also noted that most of the inactivated influenza vaccines used in the EU contain also 15 µg HA (in 0.5 ml) per viral strain.

Thus, it is agreed that the same formulation for subjects 50-64 YOA than the one currently approved for 65 years of age and olderwas tested, without performing additional dose finding studies.

2.4.2. Main study

Study V118_23

Title: A Phase 3, Randomized, Observer-blind, Controlled, Multicenter, 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; 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 MAH 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 hospitalizations due to pneumonia or influenza.

Table 1: Prediction rule for estimating the probability of hospitalization 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 (nonadjuvanted 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: 2 influenza A strains (A/H1N1 and A/H3N2) and 2 influenza B strains (B/Yamagata and B/Victoria).

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, ie, the Northern Hemisphere 2021/2022 influenza.

The composition of both vaccines is provided in the following table.

Table 2

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) Nominally 15 µg HA/strain	• 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
Adjuvant (per 0.5 mL, volume of formulation): • Squalene 9.75 mg • Polysorbate 80 1.175 mg • Sorbitan trioleate 1.175 mg • Sodium citrate 0.66 mg • Citric acid 0.04 mg	Non-adjuvanted
Other Ingredients (per 0.5 mL, volume of formulation): • Sodium chloride 4.00 mg • Potassium chloride 0.10 mg • Potassium dihydrogen phosphate 0.10 mg • Disodium phosphate dihydrate 0.67 mg • Magnesium chloride hexahydrate 0.05 mg • Calcium chloride dihydrate 0.06 mg • Water for injection up to 0.50 mL	Other Ingredients (per 0.5 mL, volume of formulation): • Sodium chloride 3.75 mg • Disodium phosphate dodecahydrate 1.3 mg • Potassium dihydrogen phosphate 0.2 mg • Potassium chloride 0.1 mg • Magnesium chloride hexahydrate Not Reported • Water for injection • Octoxynol-10 (TRITON X-100) ≤0.115 mg

	• α-tocopherol hydrogen succinate ≤0.135 mg • Polysorbate 80 (Tween 80) ≤0.550 mg

The product batch numbers of aQIV were 8552A1C (expiry date: 30 Apr 2022) for study sites in Estonia and Germany, and 316575 (expiry date: 11 May 2022) for study sites in the US.

The product batch numbers of QIV were PD237 (expiry date: 30 Jun 2022) for study sites in Estonia and Germany, and PD237 and KA92R (expiry date: 30 Jun 2022) for study sites in the US. Subjects receiving QIV at Site 84006 in the US received batch PD237; subjects receiving QIV at all other sites in the US received batch KA92R.

The study participants were individuals 50 to 64 years of age (i.e. 50 to ≤64 years), and subjects with controlled clinical conditions were allowed to participate in the trial. Those with abnormal function of the immune system were excluded. This approach was endorsed since it allows inclusion of subjects with comorbidities that put them at a higher risk of influenza complications.

The MAH 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). The comorbidity risk score assessment incorporates medical comorbidity and other baseline characteristics such as age, gender, outpatient visits during the previous year and previous hospitalizations due to pneumonia or influenza. This approach was considered acceptable although routinely, to assess the impact of comorbidities on immune response induced by vaccination, the subjects are classified in those with or without underlying chronic conditions (that put them at risk of severe influenza disease), without taking into account other baseline characteristics.

Differences in strain composition are noted for two out of the four strains in the two vaccines (aQIV and QIV) used in the pivotal trial (namely, H3N2 and B/Victoria strains). It is acknowledged that both formulations are in accordance with WHO and CHMP recommendations for quadrivalent influenza vaccines contemporaneous to the timing of the study, season 2021-2022. The MAH was asked to comment on the possible impact on the HI results obtained due to using two vaccines with different composition (regarding strains H3 and B/Victoria) in trial V118_23. As described by the Centers for Disease Control and Prevention (CDC), influenza viruses are considered to be antigenically similar or "like" each other if their HI titres differ by 2 dilutions or less (CDC 2022). Thus, given the designation of these CVVs as antigenically like by public health experts, the use of one target virus in the HI assay to represent the A/H3N2 vaccine strain and the B/Victoria vaccine strain is considered to have no major implications. However, it should be noted that the actual impact of using the vaccine strains in the HAI assay on the measured immune responses is not known, and thus, a biased GMT ratio estimate could not be formally excluded. Given that NI is clearly demonstrated, it is however agreed that this should probably not have major implications for the NI conclusion.

The MAH was asked to comment on the implications on the HI results considering that validation of the HI assay was performed on strains present in aQIV (A/Cambodia/e0826360/2020 IVR-224 (H3N2) and B/Victoria/705/2018 BVR-11 (B-Victoria lineage)) but not on the strains present in the comparator vaccine (A/Tasmania/503/2020 (IVR-221) (H3N2) and B/Washington/02/2019 (B-Victoria lineage). It is considered that this issue has no major implications in the results obtained.

It is noted that aQIV is a subunit vaccine, whereas the Comparator (QIV) is a split vaccine.

Objectives

There are no clinical efficacy objectives in this study.

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

There are no efficacy endpoints in this study.

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 titer <1:10 and a postvaccination (Day 22) HI titer ≥1:40, or with either a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer

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)

<u>SECONDARY IMMUNOGENICITY ENDPOINTS:</u>

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 postvaccination HI titer over the prevaccination HI titer (Day 22/Day 1, Day 181/Day 1)
- The percentage of subjects with a titer ⩾1:40 at Day 1, Day 22, and Day 181
- SCR: The percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ⩾1:40 or a prevaccination titer ⩾1:10 and a ⩾4-fold increase in postvaccination titer on Day 22 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. This exploratory analysis at Day 1 and Day 271 will be reported in a CSR addendum.

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 microneutralization (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). These analyses (if performed) will be reported in a (separate) CSR addendum.

As indicated, in trial V118_23, there is no clinical efficacy endpoint, but only immunological endpoints. This approach is acceptable, in agreement with current influenza virus vaccines guideline (Guideline on influenza vaccines – non-clinical and clinical Module -EMA/CHMP/VWP/457259/2014).

Immune response against the four homologous egg-derived vaccine strains was measured in terms of: 1) GMT of HI antibodies (on Day 1, Day 22, for the primary analysis, and also titers at Day 181 for some secondary analysis, and 2) SCR (seroconversion rate): the percentage of subjects with either a prevaccination HI titre <1:10 and a postvaccination HI titre ⩾1:40 or a prevaccination titre ⩾1:10 and a ⩾4-fold increase in postvaccination titre (measured on Day 22 and Day 181). The use of GMT of HI antibodies and SCRs is considered adequate to compare the immune response induced by the two vaccines. The definition used for SCR is also considered adequate and it has been used in many other immunogenicity comparisons between influenza vaccines. Moreover, the definition of SCR is considered adequate and in fact this definition was already mentioned in a previous CHMP guideline (Note for guidance on harmonization of requirements for influenza vaccines –CPMP/BWP/214/96), which is no longer in use.

The MAH established two primary objectives: The first one (1a) involves demonstration of non-inferiority of aQIV compared to QIV, for each of the four viral strains, in terms of HI GMT ratio (four comparisons, one per viral strain included in the vaccine) and the SCR difference (four comparisons, one per viral strain included in the vaccines). 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. The approach taken for endpoint 1a as well as the non-inferiority margins chosen are considered acceptable and are in line with those used in previous influenza vaccine immunogenicity comparisons.

The second primary endpoint (1b) is aimed at demonstrating that aQIV induces a superior immune response compared with QIV as measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains. The success criterion is that 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.

It is noted that the current guideline on influenza vaccines (non-clinical and clinical module EMA/CHMP/VWP/457259/2014) states:

-"*Alternatively, subject to adequate justification, Applicants could choose to conduct an active controlled study i.e. in which the control vaccine is an approved influenza vaccine. In this case the study may be designed to show superiority of the test vaccine over an authorised product (e.g. an adjuvanted vaccine vs. a non-adjuvanted vaccine). Depending on the characteristics of the test vaccine and of the selected comparator, and subject to adequate justifications, it may be acceptable to plan a primary analysis based on showing non-inferior efficacy. The choice of non-inferiority margins should be appropriately justified by the Applicant.*

"*To authorise the use of a new adjuvanted surface antigen vaccine in adults and/or the elderly an advantage in terms of immune responses is required to justify the inclusion of an adjuvant. Such advantage may be based on a demonstration of superior immunogenicity vs. a non-adjuvanted but otherwise comparable authorised vaccine that has been reviewed by EU competent regulatory authorities. An advantage for the adjuvanted vs. non-adjuvanted formulation could include a higher seroconversion rate, higher antibody titres (based on GMTs or proportions reaching a predefined cut-off titre) or other immune response parameters, including increased breadth or duration of response.*"

Taking into consideration the previous statements from the CHMP influenza vaccines guideline, the approach taken by the MAH that requires meeting the two primary objectives (non-inferiority and superiority) to support approval of aQIV for subjects from 50 to 64 YOA was considered acceptable. However, the CHMP guideline on influenza vaccines does not specify if superiority needs to be demonstrated for all four strains, but it is considered that the endpoint proposed by the MA is poorly demanding, since it only requires demonstration of superiority in terms of GMT ratio for at least 2 of the 4 vaccine strains. It is considered that optimally, superiority of aQIv vs QIV in terms of GMT ratio should have been demonstrated for the four viral strains to robustly demonstrate the role of the adjuvant in terms of inducing an increase of the immune response in comparison with a non-adjuvanted vaccine. Thus, the MAH was asked to justify the success criterion for primary endpoint 1b (aimed to demonstrate increased immune response of aQIv vs QIV) that requires showing superiority for at least two of the 4 viral strains, when optimally superiority should have been demonstrated for the four viral strains. The MAH indicated that responses to influenza vaccine strains show high variability across seasons and by strain; in particular, influenza B vaccine strains in recent years have been less immunogenic. Accordingly, a success criterion of at least 2 of the 4 viral strains being superior to the comparator vaccine represents a clinically meaningful benefit.

There are two secondary objectives (2a and 2b), that involved determining GMT ratio (QIV/aQIV) at Day 22 (2a) and 181 (2b) for the four strains included in the vaccine. In relation to endpoint 2a, Superior immune response of aQIV compared to QIV 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. Objective 2b, to demonstrate greater persistence of the immune response for at least one vaccine strain at 6 months after vaccination, being the 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."

Although the analysis of objectives 2a and 2b uses a higher threshold for superiority than that assessed in objective 1b, it is questioned the relevance of this objective from the point of view of the overall increased clinical protection provided by aQIV, since endpoint 2a can just be reached by showing superiority to only

one of the four viral strains. Similarly, meeting the secondary objective 2b (greater persistence of immune response) can be met by just showing greater persistence of immune response to just one of the four strains.

Endpoint 2c is aimed to evaluate the immunogenicity of aQIV compared with QIV as measured by HI 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 postvaccination HI titre over the prevaccination HI titre (Day 22/Day 1, Day 181/Day 1), and the percentage of subjects with a titrer ≥1:40 at Day 1, Day 22, and Day 181. This endpoint does not imply any hypothesis testing.

Exploratory objectives include persistence of the immune response of aQIV compared to QIV at day 271 as determined by HI assays, and assessment of the immunogenicity against homologous or heterologous strains by either HI or microneutralization. The MAH indicated that neutralization testing was an exploratory objective and that is currently not planned to be conducted. Results on persistence of immune response at day 271 were provided upon request by the MAH. The new data did not alter the conclusions stated.

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 randomization, 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

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 randomized 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. Stratification according to age was considered adequate.

After signing the ICF, if an individual was determined to be eligible for study participation, the investigator enrolled the subject using the IRT system. Enrolled subjects were assigned a Subject Identification (ID) and randomized in the IRT system in a 1:1 ratio to receive either aQIV or QIV with age (50 to ≤59 years/60 to ≤64 years) and history of any influenza vaccination within the previous 3 influenza seasons (yes/no) as stratification factors. Approximately 50% of subjects were to be enrolled into each age group. The list of randomization assignments was produced by the IRT service provider and approved by Seqirus according to applicable Seqirus Standard Operating Procedure (SOP).

If for any reason, after signing the ICF, a subject who was eligible and enrolled failed to be randomized, this was called a randomization failure and the early termination study procedures were applied. The information on subjects who were randomization failures was kept distinct from subjects who were screen failures.

Regarding the stratification factor "any influenza vaccination within the previous 3 influenza seasons" rather than "influenza vaccination in the previous influenza season" it was clarified that this was due the variability between countries and EU/US. Thus, the Company applies an interval of 3 influenza seasons to capture recent influenza vaccine exposure. In this study, the majority of subjects reported as previously vaccinated received their influenza vaccine in the year just prior to the year of study conduct (81% of subjects).

Blinding (masking)

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 (ie, 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 centers, remained blinded to the treatment codes until the clinical database had been locked, protocol deviations (except for Day 271 serum sample analysis protocol deviations) had been assessed, and the data released for statistical analysis. The analysis of the primary and secondary objectives for the final CSR were conducted on these data.

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. The exploratory analysis on the 9-month persistence objective will be conducted on these data and reported in a CSR addendum.

The observer-blind strategy was considered acceptable taking into account that the comparator vaccine is a commercial vaccine.

Statistical methods

General issues for statistical analyses

All EDC data up to Visit 6 (Day 271) at the time of database lock, immunogenicity serum lab samples supporting primary and secondary objectives collected up to Visit 5 (Day 181) and protocol deviations (except for Day 271 serum sample analysis PDs) will be used to support final CSR analysis.

Adjustment for Covariates

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

The main statistical analysis includes descriptive statistics for the overall population. Subgroup analyses will be done by age cohort (50-59 and 60-64 year of age), previous vaccination history, sex, race, ethnicity, and comorbidity risk scores (Hak score, <50 and ≥50). Summary tables will show unadjusted GMTs for each vaccine group by time point.

Adjusted GMTs will be calculated based on the log10-transformed antibody titers at Day 22/181/271 using an ANCOVA model which includes the vaccine group (aQIV and QIV), log10- transformed pre-vaccination

antibody titer, age cohort (50-59 or 60-64 year of age), sex, and history of any influenza vaccination within the 3 previous seasons (yes/no). The main analysis of binary immunogenicity endpoints (i.e., percentages of subjects with seroconversion) will not be adjusted for any of the covariates. Binary data will be summarized for each group using unadjusted estimates and will be reported together with two-sided 95% CIs calculated according to the Clopper-Pearson method. Sensitivity analysis may be done to include the vaccine group (aQIV and QIV), stratification factors age and previous vaccination history, and sex in a generalized linear model.

The primary methods for both primary endpoints were endorsed. However, it would have been desirable that more details had been provided on the "generalized linear model".

Handling of Dropouts, Missing Data

The distribution of subjects excluded from FAS/PPS will be described by vaccine group.

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%.

It was indicated that the reasons for missingness should be reported in detail so that, eventually, missing data may be finally considered as non-informative and complete case analysis as a valid strategy.

It may be agreed that, apparently, a low rate of missing data appears to be less prone to bias, but this is not always the case as it depends on the missing data mechanism. Therefore, a more robust plan to deal with deviations from MCAR, and to cover Missing At Random (MAR) or Missing Not At Random (MNAR) situations are not present in this study. In fact, ideally, this plan should have been primary while the complete case analysis should be considered as a sensitivity strategy. The Company was asked to clarify: in order to analyse whether missing data can play an important role with regards to the direction of the primary efficacy tests, the MAH was asked to provide a detailed description by arm of the reasons and arguments supporting the MCAR for all missing data. Also, the MAH should present an analysis of the superiority primary endpoint under the MAR assumption. This analysis should be presented also for the FAS and PPS immunogenicity populations, as well as the "complete serology dataset". These data were provided. The reasons provided by the Applicant for considering the MCAR approach as the primary analysis for handling major protocol violations and typical missing values in immunogenicity analyses (e.g., out-of-window blood draws, mishandled blood samples, insufficient quantity blood samples) are not fully supported from a methodological perspective. Ignoring the occurrence of major protocol deviations, which might be potentially related to the vaccine effect is prone to bias. Therefore, this approach does not align with the regulatory requirements of considering strategies that provide an appropriately conservative estimate in the circumstances of the trial under consideration (CPMP/EWP/1776/99 Rev. 1).

It is acknowledged that Sponsors tend to use the MCAR approach in vaccine efficacy studies due to the great magnitude of their databases. However, there is disagreement as to whether this approach might somehow mitigate the negative impact of missing data on the efficacy analysis, leading to minor differences between different strategies for handling such data (i.e., primary against sensitivity analyses). Notably, there is an inherent risk in this strategy, especially when borderline results are obtained during the efficacy analysis, as is the case in this particular study. In such situations, sensitivity analyses play a crucial role and different scenarios for the imputation of missing data must be considered to ascertain whether the robustness of the efficacy endpoint meets the regulatory standards or not.

The Applicant has presented two different approaches for the imputation of missing data, focusing on the superiority efficacy comparison of the four strains. For the FAS population, row C shows the results without imputation, row E shows the results for the worst-case scenario imputation and row F shows the results

using stochastic regression with multiple imputations. The same analyses for the PPS population are shown in rows D, G and H respectively.

Overall, the analyses performed by the MAH are welcome as they provide a context for assessing what might have happened if different strategies for dealing with missing data had been considered. However, neither of the two additional sensitivity analyses presented by the MAH provides conclusive results confirming the superiority of the experimental vaccine over the control group for any additional strain. These sensitivity analyses do not ensure that the evaluation of any additional strain besides the A/H1N1 strain (i.e. A/H3N2, B/Yamagata and B/Victoria) can be considered statistically significant, including the A/H3N2 strain itself. As a consequence of this and under a strict statistically point of view, the primary immunogenicity objective 1b (i.e. the superiority immune response of aQIV versus QIV for each strain) cannot be considered statistically significant as the success criterion for superiority was not met.

However, whether the small excess over 1 (the null effect for a ratio) at the upper limits of the GMT ratios (the higher upper limit was as of 1.08) might have a relevant impact on patient immunogenicity cannot be assessed from a purely statistical perspective.

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 randomization 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 randomized, received study vaccination and provided immunogenicity data at any time point.

In case of vaccination error, subjects in the FAS sets were analyzed "as randomized" (ie, 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 (ie, received the vaccine to which the subjects were randomized and at the scheduled time points)
- Had no protocol deviations leading to exclusion (see Appendix 16.1.1, Protocol Section 8.3.8) as defined prior to unblinding/analysis
- Were not excluded due to other reasons defined prior to unblinding or analysis (see Appendix 16.1.1, Protocol Section 8.3.8)

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 MAH 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.

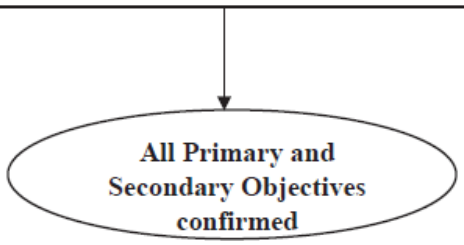
<u>Confirmatory flow of tests and objectives, using a hierarchical testing approach</u>
As soon as any success criterion is not met, confirmatory testing will stop.

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 (πQIV,i - πaQIV,i), namely,

- D1=πQIV,1 - πaQIV,1 for A/H1N1 strain
- D2=πQIV,2 - πaQIV,2 for A/H3N2 strain
- D3= πQIV,3 - πaQIV,3 for B/Yamagata strain
- D4= πQIV,4 - πaQIV,4 for B/Victoria strain

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

<u>Superiority of aQIV to QIV (Objective 1b)</u>

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.

<u>Superiority of aQIV vs QIV (higher threshold) (Objective 2a)</u>

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.

<u>Persistence of immune response of aQIV compared to QIV (Objective 2b)</u>

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.

<u>Immunogenicity of aQIV compared with QIV (Objective 2c)</u>

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

The Applicant's strategy to handle multiplicity and to control the type I error was based on a hierarchical testing approach. The first comparisons tested (primary objective 1a), correspond to co-primary non-inferiority hypotheses where, if the GMT ratio and the SCR difference are significant for all strains in the

PPS population, then the primary objective 1b will be tested. For the latter, the GTM ratio is tested and efficacy is declared if in at least 2 out of 4 strains results are significant. The rest of secondary objectives (2a and 2b) are tested hierarchically after the previous primary objectives, if applicable, for superiority for at least 1 strain and persistence for at least 1 strain with the α-adjusted CI. This approach was considered acceptable.

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 randomized in a 1:1 ratio to receive aQIV or QIV. One subject was randomized to the QIV group but did not receive study vaccine and thus the All Exposed Set included 2043 subjects.

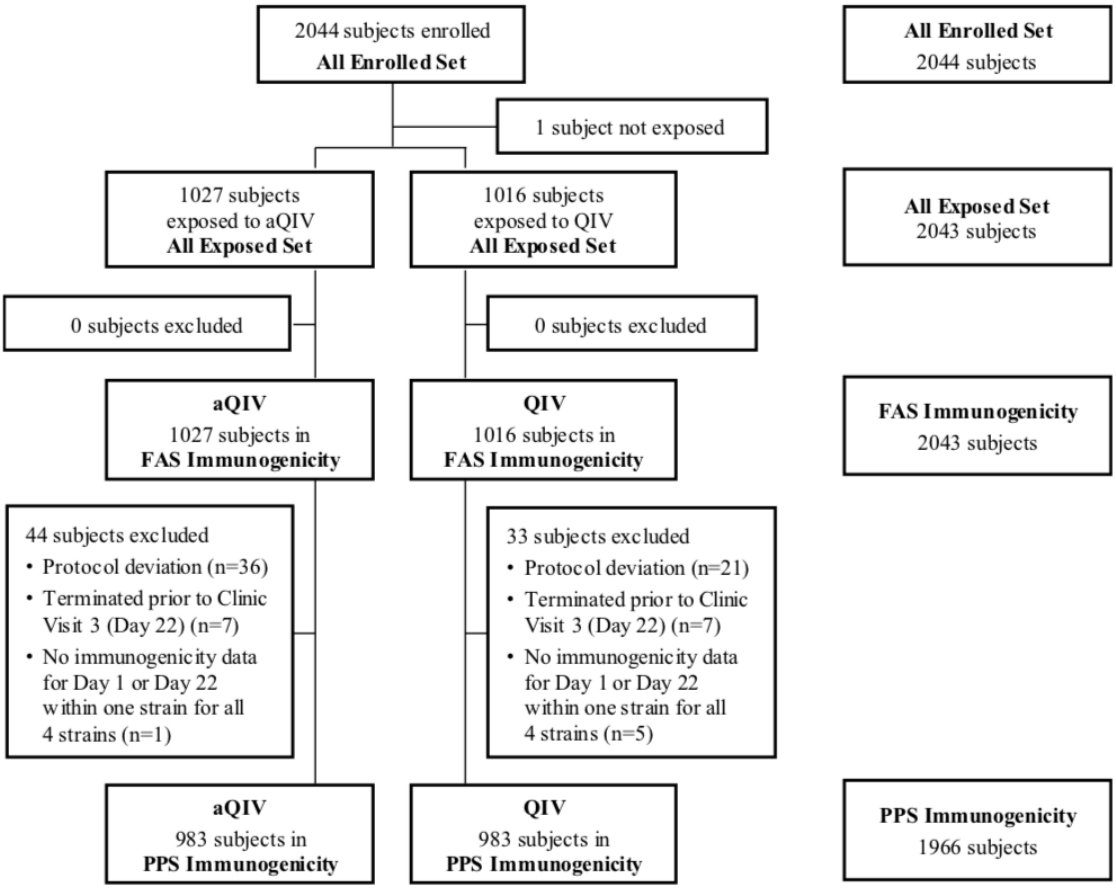
The majority of subjects (1971/2044 subjects, 96.4%) completed the study (Table 3). The most common reason for discontinuing from the study was lost to follow-up (52/2044 subjects, 2.5%).

Table 3: 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 1 here below.



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 (ie, 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 analyzed in case of vaccination errors, based on FDA regulatory agency feedback (subjects analyzed “as randomized”, as opposed to the previuos “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 labeling information for aQIV (Fluad Quadrivalent/Quad/Tetra).

Changes in the planned analyses

In the final blinded laboratory data transfer from Viroclinics for the primary and secondary immunogenicity analyses for this study, it was noted that multiple test results were reported as "Not Reportable Result" (NRR). These results were classified as "NRR-ASPECIFIC" or "NRR- INCONSISTENT". The technical laboratory personnel at Viroclinics explained that there were no further analytical options available to obtain a test result for the NRR-ASPECIFIC results. In contrast, for the NRR-INCONSISTENT results, it was identified that Viroclinics failed to follow their method SOP to retest these samples. In the final blinded laboratory dataset of Day 1, Day 22, and Day 181 results, there were NRR-INCONSISTENT results for 45 subjects across the 4 vaccine strains (A/H1N1: 25 subjects; A/H3N2: 11 subjects; B/Yamagata: 6 subjects; B/Victoria: 10 subjects). As the target enrolment level for the study had been exceeded and the drop-out rate due to premature termination and protocol deviations was smaller than anticipated, it was decided to accept the final blinded data transfer and accept that these NRR-INCONSISTENT values would be considered missing values for the initial analysis. The decision to proceed with database lock and plan to retest the NRR-INCONSISTENT samples at a later date was taken before database unblinding.

As documented in the second protocol amendment, the Day 271 samples would be tested after study unblinding as an exploratory objective. In parallel with this Day 271 testing campaign, the samples previously reported as NRR-INCONSISTENT for the primary and secondary objectives completed retesting following the Viroclinics method SOP, with the testing laboratory personnel remaining blinded to the treatment code during this testing campaign. The retesting results of samples initially reported as NRR-INCONSISTENT were transferred to Seqirus in a cumulative blinded data output comprising the complete serology dataset for Day 1, Day 22, and Day 181 after database lock and the initial statistical analysis of the primary study objectives.

Non-inferiority and superiority analyses based on the complete serology dataset, ie, inclusive of the retested NRR-INCONSISTENT samples from Day 1, Day 22, and Day 181, are presented in the CSR in together with the results based on the first analysis.

Since all the serum samples included in the complete serology dataset were assayed in a blinded fashion and the complete serology immunogenicity data were analysed in exactly the same manner as the results from the initial laboratory data transfer, these results are considered accurate and valid for analysis. Therefore, the complete serology dataset is considered a relevant dataset for the immunogenicity conclusions.

Overall, the modifications made to the protocol were not considered to introduce major changes to the original design of the trial and importantly, the protocol amendments were made while the study was still blinded.

In relation to the planned analysis, in the first analysis made by the MAH, the HI data used for the primary and secondary immunogenicity analyses excluded a number of samples (named "NRR-inconsistent" by the testing laboratory – Viroclincs-) 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 Viroclinics SOP, these samples could have been retested, the MAH 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 MAH 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)**.**

As further discussed in the results section, the MAH conducted a post-hoc sensitivity analysis based on the "Complete Serology Dataset". 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. In fact, this analysis will be considered exploratory only and no confirmatory claims can be made from these tests.

The MAH indicates 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). For clarification, the MAH was asked to detail in a table the number of samples analysed regarding primary endpoint 1b, for the first analysis and for the analysis based on the complete serology dataset for each of the four viral strains. The data should also include the number of sample analysed at the different time points (day 1, day 21 and day 181). The MAH provided information to confirm if all "NRR-Inconsistent "samples provided satisfactory results after re-analysis. It was indicated that there were no samples in the complete serology dataset with a result of "NRR-INCONSISTENT".

Table 4: Major Protocol Deviations (All Enrolled Set)

	aQIV N=1027 n (%)	QIV N=1017 n (%)	Total N=2044 n (%)
Subjects with at least one major protocol deviation	**104 (10.1)**	**81 (8.0)**	**185 (9.1)**
Procedures/Tests	80 (7.8)	62 (6.1)	142 (6.9)
Did not comply with blood draw schedule	55 (5.4)	40 (3.9)	95 (4.6)
Serological results not available	27 (2.6)	23 (2.3)	50 (2.4)
Other	17 (1.7)	10 (1.0)	27 (1.3)
Subject did not meet entry criteria	16 (1.6)	8 (0.8)	24 (1.2)
ICH GCP deviations	1 (0.1)	2 (0.2)	3 (0.1)
AE/SAE	7 (0.7)	8 (0.8)	15 (0.7)
Subject did not provide any postvaccination solicited safety data	7 (0.7)	8 (0.8)	15 (0.7)
Disallowed medications	1 (0.1)	3 (0.3)	4 (0.2)
Forbidden medication	1 (0.1)	3 (0.3)	4 (0.2)
IP administration/study treatment	1 (0.1)	2 (0.2)	3 (0.1)
Randomization error	1 (0.1)	1 (0.1)	2 (0.1)
Study vaccine not administered at all	0	1 (0.1)	1 (0.0)

Source: Table 14.1.6.

Abbreviations: AE = adverse event; aQIV = adjuvanted Quadrivalent Influenza Vaccine; GCP = Good Clinical Practice; ICH = The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IP = Investigational Product; QIV = Quadrivalent Influenza Vaccine; SAE = serious adverse event.

Note 1: The percentages are based on the number of randomized subjects in each group.

Note 2: Subjects could be included in more than one category of protocol deviation.

Note 3: The protocol deviation of "Did not comply with blood draw schedule" was reported if any of the Day 1, Day 22, Day 181, or Day 271 blood samples were taken out of window. The protocol deviation of "Serological results not available" was reported if the serological results were not available for any strain at any of the Day 1, Day 22, Day 181, or Day 271 time points.

Baseline data

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. 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. It is considered that these differences have no relevant impact in the results obtained in the trial.

Importantly, there are no notable differences in the distribution of demographic and baseline characteristics between the aQIV and QIV vaccine groups. Overall, the population included in the trial reflects the intended indication sought by the MAH.

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 5: 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/m^2)			
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).

The MAH provides information on the number of subjects that received an influenza vaccination in the previous three seasons. For completeness of the information, it was requested to provide information on the number of subjects in each arm that received a previous influenza vaccination just in the last season. The MAH clarified that 1184 subjects reported "yes" to previous influenza vaccination in the previous 3 seasons, the majority (959 subjects, 81%) reported having been vaccinated in the influenza season just

prior to when the study was conducted in the NH 2021/2022 influenza season.

Data set analysed

The numbers of subjects included in the immunogenicity analysis sets are shown in Table 6. All subjects in the All Exposed Set were included in the FAS Immunogenicity (N=2043) (Table 6, Table 7), while 77 subjects were excluded from the PPS Immunogenicity (N=1966), most commonly for protocol deviations (57 subjects) (Table 7).

Table 6: Overview of Immunogenicity Sets Analyzed (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 7: 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.

The study population (N=2044) was slightly larger than the planned sample size of 2018 subjects. Importantly, a large proportion of the enrolled subjects completed the study (95.5% of the aQIV arm and 97.2% of the QIV arm). The small difference between the two treatment arms is due to a higher number of subjects "lost to follow-up" (3.4% -aQIV- vs 1.7% -QIV).

Similarly, a large proportion (99.9%) of the subjects included in the "all enrolled set" were also included in the "FAS immunogenicity". A slightly lower percentage (96.2%) of the "all enrolled set" were included in the "PPS immunogenicity". The reasons for subjects being excluded from the "PPS immunogenicity" were similar in the two treatment arms, being the most common reason for exclusion "protocol deviation" ("did not comply with blood draw schedule", and "serological tests not available"). Within this category ("protocol deviation") there was a difference of 0.8% (16 subjects) vs 1.6% (8 subjects) between the two arms regarding the concept: "subject does not meet at least 1 inclusion or exclusion criteria".

It is noted that the evaluable subjects after protocol deviations and exclusions meet the estimated sample size for 90% of power to demonstrate the two primary endpoints (non-inferiority and superiority).

Based on all the above comments, there is no reason to question the integrity of the trial.

Outcomes and estimation

Primary endpoints

Noninferiority Analysis of aQIV Versus QIV – Geometric Mean Titer 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 8). 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 8: Postvaccination 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 9) 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 9: Complete Serology Dataset: Postvaccination 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 (Table not shown in this AR). 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. (Table not shown in this AR). 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 10). 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 10: 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 11) 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 11: 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:

- 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 (Table 8, Table 9).
- 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 (Table 10, Table 11).

The results for the first and complete serology dataset analyses of non-inferiority in the PPS Immunogenicity were consistent with the corresponding sensitivity analyses conducted in the FAS Immunogenicity. As the prespecified success criteria for Study Objective 1a were met, the study was considered successful and non-inferiority of aQIV compared with QIV in subjects 50 to 64 years of age was concluded.

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 Titer Ratios (Study Objective 1b)

In the FAS Immunogenicity first analysis (Table 12), 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 12: Postvaccination 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.

<u>Analysis on the Complete Serology Dataset: Superiority Analysis in the FAS Immunogenicity</u>

For the complete serology dataset, the point estimates of the Day 22 GMT ratios in the FAS Immunogenicity (Table 13) 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 13: Complete Serology Dataset: Postvaccination 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, ie, 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, ie, 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.

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.

The planned primary efficacy objective consisting of the two 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. Therefore, the objective of the study to demonstrate immunological efficacy according to the applicant's study design was considered met. 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 primary objective was not met, any further testing will not maintain Type I error control and will therefore be considered only exploratory and no confirmatory claims can be made from these tests. Following MAH responses this issue was considered solved.

The MAH conducted a post-hoc sensitivity analyses based on the "Complete Serology Dataset", and then, and additional strain (A/H3N2) was shown to be significant. The MAH then states that the study should be considered as positive. 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.

The issue that the study failed to meet that planned primary objective, and therefore the immunological benefit of aQIV compared to QIV in subjects from 50 to 64 yoa could not be considered positive was raised as a major objection during the procedure. After the MAH responses this issue was considered solved.

Secondary Immunogenicity Endpoints

Superiority Analysis of aQIV Versus QIV (Higher Threshold) – Geometric Mean Titer 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 (ie, 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 in Table 14 for descriptive purposes only.

Table 14: Postvaccination 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 15). 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 15: Postvaccination 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 titer ⩾1:40, and SCRs are presented for the FAS Immunogenicity in Table 16 and summarized below. The results in the complete serology dataset are consistent with the results summarized below (data not shown in this AR). No formal statistical comparisons were made between the aQIV and QIV groups.

Table 16: Pre- and Postvaccination GMT, GMFI, Percentage of Subjects with Titer ≥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.

The MAH followed a hierarchical testing approach so as soon as any success criterion is not met, confirmatory testing will stop. Thus, since Study Objective 1b was not met, confirmatory testing stopped and thus analysis of superiority of aQIV versus QIV at the higher superiority margin of 0.67 (at day 22: Study Objective 2a, and at day 181 GMTs: study objective 2b) was not conducted.

The MAH provided the secondary immunogenicity analysis for descriptive purposes only.

The descriptive data corresponding to endpoint 2c did not provide any new relevant information. In fact the results were in line with those shown regarding endpoints 1a and 1b. In fact, both at Day 22 and at day 181, the HI GMT and GMFI were observed to be higher for the A/H1N1 strain in the aQIV group compared with the QIV group and there were no notable differences in HI GMTs and GMFIs between the two vaccine groups for the A/H3N2, B/Yamagata, and B/Victoria strains. Similarly, at day 22, there were no notable differences in the SCRs between the aQIV and QIV groups for any of the 4 vaccine strains.

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 are shown graphically using RCD curves based on Day 22 HI titers in Figure 11-1, Figure 11-2, Figure 11-3, and Figure 11-4, respectively. (these figure are not provided in this AR).

The RCD curves display titer levels (x-axis) by the percentage of subjects (y-axis) having a titer value greater than or equal to the value on the x axis.

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

Subgroup Analyses for Immunogenicity: Comparison of Results in Sub-Populations

This section presents subgroup analyses of the Day 22 GMT and GMT ratio immune responses by age, previous vaccination history, sex, race, ethnicity, comorbidity risk score, and baseline HI titer for the first analysis in the FAS Immunogenicity. The results in the complete serology dataset are consistent with the subgroup analysis results summarized below (data not shown in this AR).

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 17: Postvaccination 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 18).

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 18: Postvaccination 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 titer

For subjects with a baseline titer ≥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 titer <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.

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 compared have wide 95%CI and these CI overlap for the two subgroups analysed within the two analysis made (previous history of vaccination and comorbidity score).

Summary of main study(ies)

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 19: Summary of Efficacy for trial V118_23

Title: A phase 3 randomized, observer-blind, controlled, multicenter 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 randomized: 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 randomized: 1017 subjects 50-64 years of age
Endpoints and definitions:	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

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.	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.
	Primary endpoint 1bis <u>post-hoc</u>	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 randomized, 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.
Descriptive statistics and estimate variability	

	Day 22 GMT	
	aQIV N=983 (95% CI)	QIV N=983 (95% CI)
A/H1N1	735.20 (692.28, 780.78)	587.24 (552.90, 623.70)
A/H3N2	347.75 (324.63, 372.53)	314.38 (293.54, 336.70)
B/Yamagata	154.40 (146.79, 162.41)	145.72 (138.56, 153.26)
B/Victoria	144.35 (136.89, 152.21)	143.59 (136.21, 151.37)
	Day 22 SCR	
	aQIV N=983 % (95% CI)	QIV N=983 % (95% CI)
A/H1N1	81.0 (78.37, 83.43)	76.5 (73.64, 79.10)
A/H3N2	63.4 (60.26, 66.46)	61.6 (58.44, 64.67)
B/Yamagata	43.2 (40.09, 46.43)	41.1 (37.96, 44.23)
B/Victoria	44.3 (41.10, 47.46)	40.7 (37.64, 43.89)

Effect estimate per comparison	Primary endpoint 1a	Comparison groups: QIV vs aQIV	GMT ratio (QIV/aQIV) and SCR (QIV –aQIV)
		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.	

	GMT Ratio	
	QIV over aQIV (95% CI)	Met predefined noninferiority criteria?
A/H1N1	0.80 (0.74, **0.87**)	Yes
A/H3N2	0.90 (0.82, **0.99**)	Yes
B/Yamagata	0.94 (0.88, **1.01**)	Yes
B/Victoria	0.99 (0.92, **1.07**)	Yes
	SCR Difference	
	QIV minus aQIV % (95% CI)	Met predefined noninferiority criteria?
A/H1N1	-4.5 (-8.20, **-0.89**)	Yes
A/H3N2	-1.8 (-6.12, **2.52**)	Yes
B/Yamagata	-2.2 (-6.56, **2.22**)	Yes
B/Victoria	-3.5 (-7.91, **0.87**)	Yes

	Primary endpoint 1b	Comparison groups: QIV over aQIV	GMT ratio (QIV/aQIV)
		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.	

	GMT Ratio	
	QIV over aQIV (95% CI)	Met predefined superiority criteria?
A/H1N1	0.80 (0.74, **0.87**)	Yes
A/H3N2	0.91 (0.83, **1.002**)	No
B/Yamagata	0.95 (0.88, **1.01**)	No
B/Victoria	1.00 (0.93, **1.08**)	No

	Primary endpoint 1bis	Comparison groups: QIV over aQIV	GMT ratio (QIV/aQIV)

		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.	

	GMT Ratio QIV over aQIV (95% CI)	Met predefined superiority criteria?
A/H1N1	0.81 (0.74, **0.88**)	Yes
A/H3N2	0.91 (0.83, **0.998**)	Yes
B/Yamagata	0.95 (0.88, **1.01**)	No
B/Victoria	1.00 (0.93, **1.07**)	No

Notes	The primary endpoint 1 bis was an analysis performed by the MAH 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.
Analysis description	**Secondary analysis**
	The secondary analyses were not performed since additional testing stopped after the success criterion for endpoint 1b was not met.

Supportive studies

During the assessment the MAH was asked to discuss other additional evidences to support extending the indication to subjects 50 to 64 YOA, as immunogenicity data gathered from other clinical trials performed with an influenza MF-59 adjuvanted vaccine, restricting the analysis to the population 50 to 64 YOA, immunogenicity data from other trials and effectiveness data with an influenza MF-59 adjuvanted vaccine but restricting the analysis to subjects with an age closer to the indication sought (e.g, subjects 65 to 70 yoa or 65 to 75 yoa).

As requested, the MAH provided data from RCTs and RWE studies in 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 MAH 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, and this was interpreted in the sense that the MAH did not have access to the original data of this academic study. 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 20: 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 21: 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.

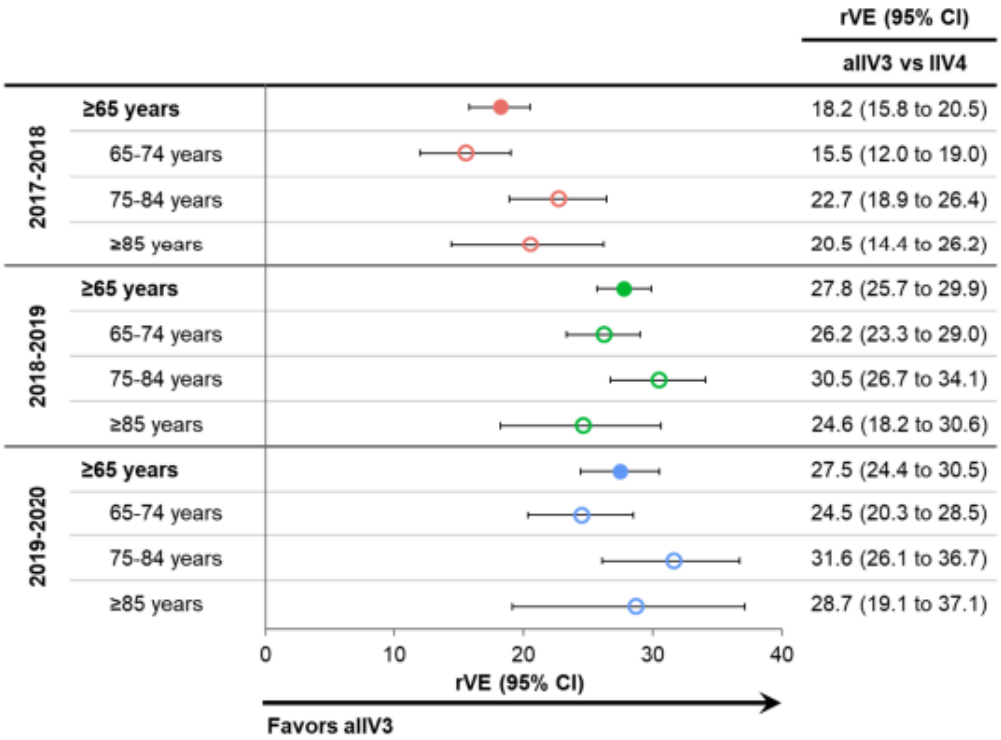
These studies were performed using an adjuvanted trivalent vaccine. However, considering that the manufacturing process and formulation of aQIV are the same as those of the adjuvanted trivalent influenza vaccine (aTIV, Fluad), with the exception of an additional B strain included in aQIV, it is considered that data obtained with aTIV can be used in support of extending the age indication for aQIV.

The new data presented in response to the RSI raised, which compare 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,) also point out in the direction of a higher immunity induced by the adjuvanted vaccine. In fact, a statistically superior GMTR is demonstrated for the three strains in trial V70P3 and for two strains in trial V7P38 and in the study by Baldo et al.

The MAH also provides 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. As requested, the MAH describes 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 IRMEs 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.

Figure 2: 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).



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.

It is noted that the comparison of aTIV vs QIV involves comparing a trivalent vs a quadrivalent vaccine, and despite this fact, the trivalent vaccine shows higher vaccine effectiveness. One of the factors that most likely influenced this result is that the B/Yamagata strain (present only in QIV) was not predominant during any of the three influenza seasons analysed.

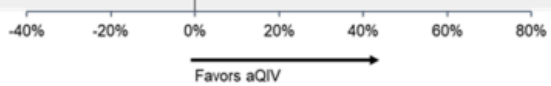
The evidence presented in these studies supports the idea of an increased effectiveness of aTIV vs non-adjunvanted vaccines in terms of reduction of influenza-related office visits among the elderly. It is noted, however, that the results from two of the mentioned retrospective cohort studies (HEOR 17-18 and HEOR 18-19) were assessed in the context of the variation procedure EMEA/H/C/004993/II/0003. It was stated then that an important weakness of these studies is that none of them used influenza-confirmed cases as primary effectiveness outcome, which is the preferred endpoint for influenza VE studies.

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 hospitalization 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 hospitalization 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.

Figure 3: 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)

Dataset		Age range (years)	Controls		Cases		Adjusted VE (95% CI)
			Vx	No Vx	Vx	No Vx	
Respiratory DataMart*	Hospital	65-74	765	1201	172	163	40% (19 to 55)
		≥65	2310	3989	446	569	27% (14 to 38)
SGSS*	Hospital	50-64	3919	220	1524	60	34% (8 to 53)
		65-74	3200	5051	1150	1311	25% (16 to 34)
		≥65	9585	17709	3121	4525	18% (13 to 23)
Primary Care Sentinel**	Primary care	65-74	264	780	40	98	23% (-34 to 56%)
		≥65	420	420	61	167	29% (-10 to 54%)



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).

2.4.3. Discussion on clinical efficacy

Introduction

Fluad Tetra (aQIV) is authorised in the EU, from May 2020, for subjects older than 65 YOA. This quadrivalent influenza vaccine contains 15 µg hemagglutinin (HA) of each influenza virus strain, including both A/H1N1 and A/H3N2 strains and strains of both B lineages. The vaccine is an egg-derived, inactivated, MF-59-adjuvanted vaccine that shows an increased immunogenicity in subjects older than 65 YOA. The clinical development program to support registration of the quadrivalent vaccine builds upon the development program of the trivalent version of the vaccine (aTIV), which was licensed for use in persons 65 years of age and older in Europe in 1997.

Considering the public health impact of severe disease caused by influenza infection in the age group 50-64 YOA (particularly in those with certain comorbidities), it is acknowledged that the MAH decided to carry out study V118_23 to assess the benefits and risks of this adjuvanted vaccine in this age group, in order to support registration of aQIV for use in persons from 50 years of age.

The MAH states that the design of the study is consistent with the EMA Guideline on Influenza Vaccines (EMA 2016) and with the CBER Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (CBER 2007).

The MAH did not seek Scientific advice at the CHMP.

The current data package includes data from Study V118_23, a randomized, comparator-controlled, observer-blind, multicenter study to evaluate the immunogenicity and safety of aQIV versus a licensed non-adjuvanted QIV comparator (QIV) in subjects 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. The clinical trial V118_23 was performed in accordance with GCP, as indicated by the MAH.

The MAH indicated that there is a planned clinical disease endpoint study with aQIV to be conducted as part of a post marketing requirement following FDA's initial approval of Fluad Quadrivalent under accelerated approval regulations: Study V118_24 – A Phase 3/3b, Randomized, Observer-blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety, and Immunogenicity of an MF59-Adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine Compared to a Quadrivalent Influenza Vaccine in Adults ≥65 Years of Age. The MAH committed to submit to EMA the results of this trial when available.

Main study V118_23

Methods

The use of the Hemagglutination Inhibition (HI) assay as the primary assay to assess vaccine immunogenicity is in agreement with the recommendations of the Guideline on Influenza Vaccines (Non-clinical and clinical module) (EMA/CHMP/VWP/457259/2014). It is also considered adequate that serum samples were analysed for HI titres both at baseline (before vaccination) and at day 21 post-vaccination.

In agreement with the CHMP guideline, all samples were tested for HI antibodies at one central laboratory (Viroclinics Biosciences BV, Rotterdam, The Netherlands). The data submitted support the adequate validation of the HI assay.

The vaccine tested in trial V118_23 contains the influenza hemagglutinin (HA) antigen from four viral strains grown in eggs, and the adjuvant MF-59. The dose (0.5 ml) of 15 µg HA per viral strain is in agreement with the Eur. Ph. requirements. This same composition is the one currently approved for use in subjects 65 YOA and older, and it is also noted that most of the inactivated influenza vaccines used in the EU contain also 15 µg HA (in 0.5 ml) per viral strain. Thus, it makes sense that the MAH tested the same formulation for

subjects 50-64 YOA than the one currently approved for ≥65YOA, without performing additional dose finding studies.

The study participants were individuals 50 to 64 years of age (i.e. 50 to ≤64 years), and subjects with controlled clinical conditions were allowed to participate in the trial. Those with abnormal function of the immune system were excluded. This approach is endorsed since it allows inclusion of subjects with comorbidities that put them at a higher risk of influenza complications.

It is noted that the MAH has 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). The comorbidity risk score assessment incorporates medical comorbidity and other baseline characteristics such as age, gender, outpatient visits during the previous year and previous hospitalizations due to pneumonia or influenza. This approach is considered acceptable although routinely, to assess the impact of comorbidities on immune response induced by vaccination, the subjects are classified in those with or without underlying chronic conditions (that put them at risk of severe influenza disease), without taking into account other baseline characteristics.

Differences in strain composition are noted for two out of the four strains in the two vaccines (aQIV and QIV) used in the pivotal trial (namely, H3N2 and B/Victoria strains). It is acknowledged that both formulations are in accordance with WHO and CHMP recommendations for quadrivalent influenza vaccines contemporaneous to the timing of the study, season 2021-2022. The MAH was asked to comment on the possible impact on the HI results obtained due to using two vaccines with different composition (regarding strains H3 and B/Victoria) in trial V118_23. The MAH provided a satisfactory answer and it is considered that this issue has no major implications in the results obtained. However, it should be noted that the actual impact of using the vaccine strains in the HAI assay on the measured immune responses is not known, and thus, a biased GMT ratio estimate could not be formally excluded. Given that NI is clearly demonstrated (see below), it is however agreed that this should probably not have major implications for the NI conclusion.

It is noted that aQIV is a subunit vaccine, whereas the comparator (QIV) is a split vaccine.

Objectives

In trial V118_23, there is no clinical efficacy endpoint, but only immunological endpoints. This approach was considered acceptable, in agreement with current influenza virus vaccines guideline (Guideline on influenza vaccines – non-clinical and clinical Module -EMA/CHMP/VWP/457259/2014).

Immune response against the four homologous egg-derived vaccine strains was measured in terms of: 1) GMT of HI antibodies (on Day 1, Day 22, for the primary analysis, and also titers at Day 181 for some secondary analysis, and 2) SCR (seroconversion rate): the percentage of subjects with either a prevaccination HI titre <1:10 and a postvaccination HI titre ≥1:40 or a prevaccination titre ≥1:10 and a ≥4-fold increase in postvaccination titer (measured on Day 22 and Day 181). The use of GMT of HI antibodies and SCRs are considered adequate to compare the immune response induced by the two vaccines. The definition used for SCR is also considered adequate and it has been used in many other immunogenicity comparisons between influenza vaccines. Moreover, the definition of SCR was in fact the definition already mentioned in a previous CHMP guideline (Note for guidance on harmonization of requirements for influenza vaccines –CPMP/BWP/214/96), which is no longer in use.

The MAH establishes two primary objectives: The first one (1a) involves demonstration of non-inferiority of aQIV compared to QIV, for each of the four viral strains, in terms of HI GMT ratio (four comparisons, one per viral strain included in the vaccine) and the SCR difference (four comparisons, one per viral strain included in the vaccines). 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. The approach taken for endpoint 1a as well as the non-inferiority margins chosen are considered acceptable and are in line with those used in previous influenza vaccine immunogenicity comparisons.

The second primary endpoint (1b) is aimed at demonstrating that aQIV induces a superior immune response compared with QIV as measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains. The success criterion is that 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.

It is noted that the current guideline on influenza vaccines (non-clinical and clinical module EMA/CHMP/VWP/457259/2014) states:

-"*Alternatively, subject to adequate justification, Applicants could choose to conduct an active controlled study i.e. in which the control vaccine is an approved influenza vaccine. In this case the study may be designed to show superiority of the test vaccine over an authorised product (e.g. an adjuvanted vaccine vs. a non-adjuvanted vaccine). Depending on the characteristics of the test vaccine and of the selected comparator, and subject to adequate justifications, it may be acceptable to plan a primary analysis based on showing non-inferior efficacy. The choice of non-inferiority margins should be appropriately justified by the Applicant.*

"*To authorise the use of a new adjuvanted surface antigen vaccine in adults and/or the elderly an advantage in terms of immune responses is required to justify the inclusion of an adjuvant. Such advantage may be based on a demonstration of superior immunogenicity vs. a non-adjuvanted but otherwise comparable authorised vaccine that has been reviewed by EU competent regulatory authorities. An advantage for the adjuvanted vs. non-adjuvanted formulation could include a higher seroconversion rate, higher antibody titres (based on GMTs or proportions reaching a predefined cut-off titre) or other immune response parameters, including increased breadth or duration of response.*"

Taking into consideration the previous statements from the CHMP influenza vaccines guideline, the approach taken by the MAH that requires meeting the two primary objectives (non-inferiority and superiority) to support approval of aQIV for subjects from 50 to 64 YOA is considered acceptable. However, the CHMP guideline on influenza vaccines does not specify if superiority needs to be demonstrated for all four influenza strains, but it is considered that the endpoint proposed by the MA is poorly demanding, since it only requires demonstration of superiority in terms of GMT ratio for at least 2 of the 4 vaccine strains. It is considered that optimally, superiority of aQIv vs QIV in terms of GMT ratio should have been demonstrated for the four viral strains to robustly demonstrate the role of the adjuvant in terms of inducing an increase of the immune response in comparison with a non-adjuvanted vaccine. Thus, the MAH was asked to justify the success criterion for primary endpoint 1b (aimed to demonstrate increased immune response of aQIv vs QIV) that requires showing superiority for at least two of the 4 viral strains, when optimally superiority should have been demonstrated for the four viral strains. The MAH indicated that responses to influenza vaccine strains show high variability across seasons and by strain; in particular, influenza B vaccine strains in recent years have been less immunogenic. Accordingly, a success criterion of at least 2 of the 4 viral strains being superior to the comparator vaccine represents a clinically meaningful benefit.

Although it is agreed that responses to influenza vaccine strains show high variability across seasons and by strain, it is unclear why this fact should impact on not achieving superiority of the MF59 adjuvanted vaccine against all four viral components. Certainly, a success superiority criterion of at least 2 of the 4 viral implies a clinical benefit, but this benefit, as compared to a non-adjuvanted vaccine, disappears in seasons in which the predominant circulating strains are those which show the same immune response wherever the vaccine is adjuvanted or not.

Altogether the data provided are considered sufficient to approve the current variation procedure, and thus this issue related to this question is not further pursued.

There are two secondary objectives (2a and 2b), that involved determining GMT ratio (QIV/aQIV) at Day 22 (2a) and 181 (2b) for the four strains included in the vaccine. In relation to endpoint 2a, Superior immune response of aQIV compared to QIV 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. Objective 2b, to demonstrate greater persistence of the immune response for at least one vaccine strain at 6 months after vaccination, being the 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."

Although the analysis of objectives 2a and 2b uses a higher threshold for superiority than that assessed in objective 1b, it is questioned the relevance of this objective from the point of view of the overall increased clinical protection provided by aQIV, since endpoint 2a can just be reached by showing superiority to only one of the four viral strains. Similarly, meeting the secondary objective 2b (greater persistence of immune response) can be met by just showing greater persistence of immune response to just one of the four strains.

Endpoint 2c is aimed to evaluate the immunogenicity of aQIV compared with QIV as measured by HI 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 postvaccination HI titre over the prevaccination HI titre (Day 22/Day 1, Day 181/Day 1), and the percentage of subjects with a titre ≥1:40 at Day 1, Day 22, and Day 181. This endpoint does not imply any hypothesis testing.

Exploratory objectives include persistence of the immune response of aQIV compared to QIV at day 271 as determined by HI assays, and assessment of the immunogenicity against homologous or heterologous strains by either HI or microneutralization. The MAH indicated that neutralization testing was an exploratory objective and that is currently not planned to be conducted. Results on persistence of immune response at day 271 were provided upon request by the MAH. The new data do not alter the conclusions stated in the first assessments report.

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 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.

Enrolled subjects were randomized in a 1:1 ratio to receive either aQIV or QIV with age (50 to ≤59 years/60 to ≤64 years) and history of any influenza vaccination within the previous 3 influenza seasons (yes/no) as stratification factors. Stratification according to age was considered adequate. A clarification is asked to the MAH in relation to stratification according to "history of any influenza vaccination within the previous 3 influenza seasons (yes/no)". The MAH was asked to elaborate on the rationale to consider as a stratification factor "any influenza vaccination within the previous 3 influenza seasons" rather than "influenza vaccination in the previous influenza season". This issue was solved and the MAH also indicated that the majority of subjects reported as previously vaccinated received their influenza vaccine in the year just prior to the year of study conduct (81% of subjects).

The study was an observer-blind study. During the treatment period of the study, designated and trained personnel 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

(blinded study personnel) involved in the monitoring of conduct of the trial. Thus, the observer-blind strategy is considered acceptable taking into account that the comparator vaccine is a commercial vaccine.

Statistical methods

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

The approach proposed by the MAH implies: 1) using the FAS immunogenicity for testing the objective 1b, and for testing the sensitivity analyses regarding objective 1a; 2) using the PPS immunogenicity for the 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 is considered acceptable.

The Applicant strategy to handle multiplicity and to control the type I error is based on a hierarchical testing approach. The first comparisons tested (primary objective 1a), correspond to co-primary non-inferiority hypotheses where, if the GMT ratio and the SCR difference are significant for all strains in the PPS population, then the primary objective 1b will be tested. For the latter, the GMT ratio is tested and efficacy is declared if in at least 2 out of 4 strains results are significant. The rest of secondary objective (2a and 2b) are tested hierarchically after the previous primary objectives, if applicable, for superiority for at least 1 strain and persistence for at least 1 strain with the α-adjusted CI. This approach is considered acceptable.

Overall, the primary statistical methods for both primary endpoints are endorsed.

Results

Two protocol amendments were made during the study. Overall, the modifications made to the protocol were not considered to introduce major changes to the original design of the trial and importantly, the protocol amendments were made while the study was still blinded.

In relation to the planned analysis, in the first analysis made by the MAH, the HI data used for the primary and secondary immunogenicity analyses excluded a number of samples (named "NRR-inconsistent" by the testing laboratory – Viroclincs-) 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 Viroclinics SOP, these samples could have been retested, the MAH 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 MAH decided to retest (in a blinded manner) the "NRR-inconsistent" serum samples. The primary and secondary analyses were then recalculated taken into account these new additional samples (analysis on the complete serology dataset)**.**

As further discussed below, the MAH conducted a post-hoc sensitivity analysis based on the "Complete Serology Dataset". 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. In fact, this analysis will be considered exploratory only and no confirmatory claims can be made from these tests.

The MAH indicates that the additional samples included in the complete serology dataset corresponded to 45 subjects across the 4 vaccine strains. For clarification, it is asked to the MAH to detail in a Table the number of samples analysed regarding primary endpoint 1b, for the first analysis and for the analysis based on the complete serology dataset for each of the four viral strains. The data should also include the number of samples analysed at the different time points (day 1, day 21 and day 181). The MAH should also confirm that all "NRR-Inconsistent "samples provided satisfactory results after re-analysis.

The study population (N=2044) was slightly larger than the planned sample size of 2018 subjects. Importantly, a large proportion of the enrolled subjects completed the study (95.5% of the aQIV arm and 97.2% of the QIV arm). The small difference between the two arms is due to a higher number of subjects "lost to follow-up" (3.4% -aQIV- vs 1.7% -QIV).

Similarly, a large proportion (99.9%) of the subjects included in the "all enrolled set" were also included in the "FAS immunogenicity". A slightly lower percentage (96.2%) of the "all enrolled set" were included in the "PPS immunogenicity". The reasons for subjects being excluded from the "PPS immunogenicity" were similar in the two treatment arms, being the most common reason for exclusion "protocol deviation" ("did not comply with blood draw schedule", and "serological tests not available"). Within this category ("protocol deviation") there was a difference of 0.8% (16 subjects) vs 1.6% (8 subjects) between the two arms regarding the concept: "subject does not meet at least 1 inclusion or exclusion criteria".

It is noted that the evaluable subjects after protocol deviations and exclusions meet the estimated sample size for 90% of power to demonstrate the two primary endpoints (non-inferiority and superiority).

Based on all the above comments, there is no reason to question the integrity of the trial.

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. 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. It is considered that these differences have no relevant impact in the results obtained in the trial.

Importantly, there are no notable differences in the distribution of demographic and baseline characteristics between the aQIV and QIV vaccine groups. Overall, the population included in the trial reflects the intended indication sought by the MAH.

The MAH provided information on the number of subjects that received an influenza vaccination in the previous three seasons. For completeness of the information the MAH provided information on the number of subjects in each arm that received a previous influenza vaccination in just the last season. It was clarified that 1184 subjects reported "yes" to previous influenza vaccination in the previous 3 seasons, the majority (959 subjects, 81%) reported having been vaccinated in the influenza season just prior to when the study was conducted in the NH 2021/2022 influenza season.

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 noninferiority 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 noninferiority 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.

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; and 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 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 efficacy objective consisting of the two 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 primary objective was not met, any further testing will not maintain Type I error control and will therefore be considered only exploratory and no confirmatory claims can be made from these tests.

The MAH conducted a post-hoc sensitivity analyses based on the "Complete Serology Dataset", and then, and additional strain (A/H3N2) was shown to be significant. The MAH then stated that the study should be considered as positive. 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.

In conclusion, the study failed to meet all of the planned primary objectives. The results from trial V118_23 (in subjects 50 to 64 yoa), which are the basis for this variation application, demonstrated non-inferiority of aQIV vs QIV (in terms of SCR differences and GMT titres) for all four viral strains. The estimates of GMT titres and SRC rates were always higher for those receiving aQIV than those that received QIV. However, this increase in the immune response elicited by the adjuvanted vaccine did only translate, in the first immunogenicity analysis, in showing superiority (in terms of GMTR) against one viral strain (H1N1), although it is noted that the results for A/H3N2 strain marginally exceeded the predefined criterion. An additional post-hoc analysis ("complete serology set") which incorporated additional serum samples, showed superior immune response of aQIV versus QIV for 2 of the 4 vaccine strains. The MAH provided new data that include the results from three RCTs and from retrospective cohort studies and public health surveillance.

The new data presented, which compare 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 point 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 MAH provided evidence from retrospective cohort studies and one public health surveillance study (carried out by the United Kingdom Health Security Agency –UKHSA-) that also indicate adequate vaccine effectiveness of the MF-59 adjuvanted vaccine in the 50-64 and in the 65-74 years age group. This latter age group is the closest one to the sought age indication of 50 to 64 years. In the retrospective cohort studies, the relative vaccine effectiveness of aTIV vs QIV for the prevention of influenza-related medical encounters favoured aTIV. 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. Regarding the UKHSA study, when using the outcome of laboratory-confirmed influenza hospitalisation, the adjusted vaccine effectiveness for aQIV ranged from 25% (95% CI: 16 to 34) to 40% (95% CI: 19 to 55) in the 65-74 years age group. Moreover, results for the 50-64 years age group demonstrated an adjusted vaccine effectiveness for aQIV against laboratory-confirmed influenza hospitalisation of 34% (95% CI: 8 to 53).

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 current variation procedure that seeks extending the indication to the 50-64 years age group.

The MAH followed a hierarchical testing approach so as soon as any success criterion is not met, confirmatory testing will stop. Thus, since Study Objective 1b was not met, confirmatory testing stopped and thus analysis of superiority of aQIV versus QIV at the higher superiority margin of 0.67 (at day 22: Study Objective 2a, and at day 181 GMTs: study objective 2b) was not conducted.

The descriptive data corresponding to endpoint 2c did not provide any new relevant information. In fact, the results were in line with those shown regarding endpoints 1a and 1b. In fact, both at Day 22 and at day 181, the HI GMT and GMFI were observed to be higher for the A/H1N1 strain in the aQIV group compared with the QIV group and there were no notable differences in HI GMTs and GMFIs between the two vaccine groups for the A/H3N2, B/Yamagata, and B/Victoria strains. Similarly, at day 22, there were no notable differences in the SCRs between the aQIV and QIV groups for any of the 4 vaccine strains.

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 have wide 95%CI and these CI overlap for the two subgroups analysed within the two analysis made (previous history of vaccination and comorbidity score).

2.4.4. Conclusions on the clinical efficacy

Study V118_23 was a randomized, comparator-controlled, observer-blind, multicenter study to evaluate the immunogenicity and safety of aQIV versus a licensed non-adjuvanted QIV comparator (QIV) in subjects 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.

Non-inferiority of aQIV vs QIV in terms of SCR differences and GMT titres was demonstrated for the four influenza viral strains (primary endpoint 1a). However, the primary endpoint 1b that required demonstrating superior response of aQIV in terms of GMT for at least 2 of the influenza viral strains was not met. The additional post-hoc analysis regarding endpoint 1b, that showed superior immune response of aQIV versus QIV for 2 of the 4 vaccine strains (A/H1N1 and A/H3N2), was not considered valid in principle to rescue the first failed analysis from a methodological and statistical point of view.

The MAH provided new data that include the results from three RCTs and from retrospective cohort studies and public health surveillance. The RCTs compare the immune response of an MF-59 adjuvanted trivalent influenza vaccine vs a non-adjuvanted one, and the results indicate overall a higher immune response of the MF-59 adjuvanted vaccines compared to the non-adjuvanted ones in the age group 50 to 64 yoa. Moreover, evidence from retrospective cohort studies and public health surveillance also indicate adequate vaccine effectiveness of the MF-59 adjuvanted vaccine in the 50-64 and in the 65-74 years age group. This latter age group is the closest one to the sought age indication of 50 to 64 years. 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 current variation procedure that seeks extending the indication to the 50-64 years age group.

2.5. Clinical safety

Introduction

The vaccine aQIV is an egg-derived inactivated subunit quadrivalent influenza virus vaccine adjuvanted with MF59 authorised in the EU for use in adults aged 65 years and over.

Overall, the aQIV safety profile in elderly adults (≥65 years of age) would be in general comparable to that of the aTIV comparators and no safety signal has been observed in this population.

The aim of this variation (EMEA/H/C/004993/II/0043) was the registration of aQIV for use in persons 50 years of age and older based on the data generated in clinical study V118_23.

Patient exposure

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.

Demographic and baseline characteristics

The mean age of the Overall Safety Set was 57.8 years. The study intended to enrol approximately 50% of subjects per age cohort; however, more subjects were enrolled in the 50 to ≤59 years of age cohort (59.0%) than the 60 to ≤64 years of age cohort (41.0%).

More female subjects (61.2%) than male subjects (38.8%) were enrolled in the study. The majority of subjects were White (95.6%) and of "Not Hispanic or Latino" ethnicity (98.5%). More than half of the subjects had received an influenza vaccination in the previous 3 influenza seasons (57.9%). The majority

of subjects had a comorbidity risk score <50 (89.6%), suggesting a lower probability of hospitalization due to pneumonia or influenza or death.

There were no notable differences in the distribution of demographic and baseline characteristics between the aQIV and QIV vaccine groups.

Table 22: Demographics and Baseline Characteristics in Subjects 50 to 64 Years of Age (All Enrolled Set[a])

	aQIV N=1027	QIV N=1017	Total N=2044
Age (years)			
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 [%])			
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 [%])			
Male	392 (38.2)	402 (39.5)	794 (38.8)
Female	635 (61.8)	615 (60.5)	1250 (61.2)
Race (n [%])			
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 [%])			
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 [%])			
Yes	586 (57.1)	598 (58.8)	1184 (57.9)
No	441 (42.9)	419 (41.2)	860 (42.1)
Comorbidity risk score[b] (n [%])			
<50	912 (88.8)	919 (90.4)	1831 (89.6)
≥50	115 (11.2)	98 (9.6)	213 (10.4)
Body mass index (kg/m^2)			
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 [%])			
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: Section 5.3.5.1, V118_23 CSR.

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

[a] The All Enrolled Set is displayed according to the randomized treatment.

	aQIV N=1027	QIV N=1017	Total N=2044

[b] 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.

Medical History

At least 1 medical disorder was reported as medical history for 88.4% of participants. The proportion of subjects with medical disorders was similar between the aQIV (87.5%) and QIV (89.3%) groups. Hypertension was the most frequently reported medical history condition (reported in 40.1% of subjects overall); all other medical history conditions occurred at a frequency of less than 15%.

Concomitant Use of Medications

During the study (Day 1 through Day 271), use of at least 1 concomitant medication was reported by 92.5% of participants. The use of concomitant medications was similar between the aQIV group (92.0%) and the QIV group (92.9%). The most commonly reported types of concomitant medication were vaccines, mainly COVID-19 vaccines (aQIV: 60.0%; QIV: 58.6%) and agents acting on the renin-angiotensin system (aQIV: 31.5%; QIV: 33.8%).

The Overall Safety Set for the study V118_23 was 2043 participants aged 50-64 years of age. Of these, 1027 participants received aQIV and 1016 participants received QIV.

The demographic and baseline characteristics were generally comparable between vaccines. However, there were enrolled more female subjects (61.2%) than male subjects (38.8%) and more subjects in the range age 50-59years (59.0%) than in 60-64 years (41.0%). It is known that age and sex could affect the reactogenicity profile in vaccines. Nevertheless, the same percentage of male/female and younger/older was observed in both groups, therefore the possible contribution of baseline characteristics to the reactogenicity profile would be similar in both groups.

In addition, the majority of subjects had a comorbidity risk score <50 (89.6%), suggesting a lower probability of hospitalization due to pneumonia or influenza or death. A high percentage of participants (88.4%) reported at least 1 medical disorder as medical history. Hypertension was the most frequently reported medical history condition (40.1%); all other medical history conditions occurred at a frequency of less than 15%.

Furthermore, 92.5% of participants received at least 1 concomitant medication during the study (Day 1 through Day 271), mainly COVID vaccines (60% approx.) and agents acting on the renin-angiotensin system (32% approx.).

Adverse events

Solicited adverse events

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 local Adverse Events

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.

Table 23: Number (%) of Subjects 50 to 64 Years of Age with Solicited Local Adverse Events from Day 1 Through Day 7 (Solicited Safety Set)

Solicited Adverse Event	aQIV N=1020 n (%)	QIV N=1008 n (%)
Induration		
Any	81 (7.9)	35 (3.5)
Severe	1 (0.1)	0
Erythema		
Any	80 (7.8)	31 (3.1)
Severe	4 (0.4)	0
Ecchymosis		
Any	6 (0.6)	6 (0.6)
Severe	0	0
Pain		
Any	480 (47.1)	283 (28.1)
Severe	1 (0.1)	3 (0.3)

Source: Section 5.3.5.1, V118_23 CSR.
Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; QIV = quadrivalent influenza vaccine.
Note 1: For induration, erythema, and ecchymosis, severe was defined as >100 mm; for pain, severe was defined as "Prevents daily activity".

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.

Solicited systemic Adverse Events

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.

Table 24: Number (%) of Subjects 50 to 64 Years of Age with Solicited Systemic Adverse Events from Day 1 Through Day 7 (Solicited Safety Set)

Solicited Adverse Event	aQIV N=1020 n (%)	QIV N=1008 n (%)
Loss of appetite		
Any	62 (6.1)	48 (4.8)
Severe	2 (0.2)	4 (0.4)
Nausea		
Any	74 (7.3)	44 (4.4)
Severe	1 (0.1)	0
Fatigue		
Any	301 (29.5)	245 (24.3)
Severe	7 (0.7)	10 (1.0)
Myalgia		
Any	133 (13.0)	73 (7.2)
Severe	4 (0.4)	4 (0.4)
Arthralgia		
Any	140 (13.7)	95 (9.4)
Severe	4 (0.4)	6 (0.6)
Headache		
Any	226 (22.2)	206 (20.4)
Severe	0	5 (0.5)
Chills		
Any	67 (6.6)	55 (5.5)
Severe	1 (0.1)	3 (0.3)
Vomiting		
Any	3 (0.3)	10 (1.0)
Severe	0	0
Diarrhea		
Any	81 (7.9)	71 (7.0)
Severe	0	2 (0.2)
Fever		
Any (≥38.0°C)	26 (2.5)	17 (1.7)
Severe (≥39.0°C)	8 (0.8)	4 (0.4)

Source: Section 5.3.5.1, V118_23 CSR.

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; QIV = quadrivalent influenza vaccine.

Note 1: For loss of appetite, severe was defined as not eating at all; for nausea, fatigue, myalgia, arthralgia, headache, and chills, severe was defined as "Prevents daily activity"; for vomiting, severe was defined as 6 or more times per 24 hours or requires intravenous hydration; for diarrhea, severe was defined as 6 or more loose stools per 24 hours or requires intravenous hydration; for fever, severe was defined as ≥39.0°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.

The number of participants evaluated for solicited AEs was 2028 subjects (1020 subjects in aQIV group and 1008 subjects in QIV group).

Any Solicited AEs were reported by 65.9% vs 53.7% of the evaluated participants, within the first 7 days aQIV or QIV treatment, respectively.

The percentage of subjects reporting solicited local AEs tended to be higher in the aQIV group than the QIV group (49.8% vs 30.4%). The most frequently reported solicited local was injection site pain (47.1% vs 28.1%), followed by induration (7.9% vs 3.5%) and erythema (7.8% vs 3.1%). The majority of solicited local AEs reported were mild or moderate in severity being reported on Day 1 or Day 2. In addition, most of solicited local AEs reported were observed in ≤3 days.

Incidence of each severe solicited local AEs was very low, the highest frequency was 0.4% for erythema in aQIV (vs 0% in QIV) and 0.3% for pain in QIV (vs 0.1% in aQIV).

The percentage of subjects reporting solicited systemic AEs were similar between aQIV group and QIV group (45.3% vs 40.0%). The most frequently solicited systemic AEs in both aQIV and QIV groups were fatigue (29.5% vs 24.3%, respectively) and headache (22.2% vs 20.4%), followed by myalgia (13.0% vs 7.2%) and arthralgia (13.7% vs 9.4%). Fever (≥38.0°C) was reported with low frequency in both aQIV and QIV groups respectively (2.5% and 1.7%). The majority of solicited systemic AEs were mild or moderate in severity with onset most commonly reported on Day 1 or Day 2. In both vaccine groups, most of solicited systemic AEs were observed in ≤3 days.

The frequency of severe solicited systemic AEs was 2.2% in both vaccine groups. Additionally, severe fever (≥39.0ºC) was reported by 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.

Unsolicited adverse events

All 2043 subjects in the Overall Safety Set had unsolicited AE data and were included in the Unsolicited Safety Set.

A summary of unsolicited AEs within 21 days following vaccination is presented in the table below. 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.

Table 25: Overall Summary of Number (%) of Subjects with Unsolicited Adverse Events in Subjects 50 to 64 Years of Age (Unsolicited Safety Set)

Unsolicited Adverse Event	aQIV N=1027 n (%)	QIV N=1016 n (%)
Day 1 through Day 22		
Any AE	169 (16.5)	172 (16.9)
Mild	116 (11.3)	115 (11.3)
Moderate	51 (5.0)	50 (4.9)
Severe	2 (0.2)	7 (0.7)
Related AE	33 (3.2)	32 (3.1)
Day 1 through Day 271		
SAE	31 (3.0)	31 (3.1)
Related SAE	0	1 (0.1)
AE leading to study withdrawal	0	1 (0.1)
AESI	2 (0.2)	0
Death	1 (0.1)	0

Source: Section 5.3.5.1, V118_23 CSR.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; aQIV = adjuvanted Quadrivalent Influenza Vaccine; QIV = quadrivalent influenza vaccine; SAE = serious adverse event.

In both vaccine groups, unsolicited AEs were most commonly categorized 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 (Table 24).

Table 26: Number (%) of Subjects 50 to 64 Years of Age with Any Unsolicited Adverse Events with Onset from Day 1 Through Day 22 by System Organ Class and Preferred Term Occurring in >1% of Subjects in Any Vaccine Group (Unsolicited Safety Set)

Preferred Term	aQIV N=1027 n (%)	QIV N=1016 n (%)
Any AE	**169 (16.5)**	**172 (16.9)**
Infections and infestations	**64 (6.2)**	**63 (6.2)**
Nasopharyngitis	16 (1.6)	10 (1.0)
Rhinitis	15 (1.5)	11 (1.1)
Nervous system disorders	**15 (1.5)**	**17 (1.7)**
Headache	10 (1.0)	13 (1.3)

Source: Section 5.3.5.1, V118_23 CSR.

Abbreviations: AE = adverse event; aQIV = adjuvanted Quadrivalent Influenza Vaccine; QIV = quadrivalent influenza vaccine.

In both vaccine groups, related unsolicited AEs were most commonly categorized 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 (Table 25).

Table 27: Number (%) of Subjects 50 to 64 Years of Age with Related Unsolicited Adverse Events with Onset from Day 1 Through Day 22 by System Organ Class and Preferred Term Occurring in ≥2 Subjects in Any Vaccine Group (Unsolicited Safety Set)

Preferred Term	aQIV N=1027 n (%)	QIV N=1016 n (%)
Any related AE	**33 (3.2)**	**32 (3.1)**
General disorders and administration site conditions	**10 (1.0)**	**10 (1.0)**
Injection site pain	3 (0.3)	1 (0.1)
Axillary pain	2 (0.2)	0
Fatigue	2 (0.2)	1 (0.1)
Injection site rash	0	2 (0.2)
Malaise	0	2 (0.2)
Musculoskeletal and connective tissue disorders	**6 (0.6)**	**4 (0.4)**
Arthralgia	2 (0.2)	1 (0.1)
Myalgia	0	2 (0.2)
Blood and lymphatic system disorders	**3 (0.3)**	**1 (0.1)**
Lymphadenopathy	3 (0.3)	1 (0.1)
Gastrointestinal disorders	**3 (0.3)**	**2 (0.2)**
Abdominal pain upper	2 (0.2)	1 (0.1)
Infections and infestations	**3 (0.3)**	**4 (0.4)**
Nasopharyngitis	1 (0.1)	2 (0.2)
Rhinitis	1 (0.1)	2 (0.2)
Nervous system disorders	**3 (0.3)**	**3 (0.3)**
Headache	2 (0.2)	2 (0.2)
Skin and subcutaneous tissue disorders	**3 (0.3)**	**1 (0.1)**
Ear and labyrinth disorders	**1 (0.1)**	**3 (0.3)**
Vertigo	1 (0.1)	3 (0.3)
Metabolism and nutrition disorders	**1 (0.1)**	**2 (0.2)**
Decreased appetite	1 (0.1)	2 (0.2)
Respiratory, thoracic, and mediastinal disorders	**1 (0.1)**	**3 (0.3)**
Vascular disorders	**1 (0.1)**	**2 (0.2)**

Source: Section 5.3.5.1, V118_23 CSR.
Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; QIV = quadrivalent influenza vaccine.

Unsolicited AEs within 21 days after vaccination were reported with low and similar frequencies in aQIV and QIV. Specifically, the unsolicited AEs were reported by 16.5% in aQIV and 16.9% in QIV, being the related unsolicited AEs observed in 3.2% and 3.1% respectively. The majority of AEs were assessed as mild or moderate in severity in both vaccine groups. Few subjects reported severe AEs (0.2% vs 0.7%), but data of incidence of severe unsolicited AEs considered as related to the study vaccine are lacking. The MAH reported that there was only one severe event reported until 28 days after the QIV administration considered related and no case in aQIV group.

The related unsolicited AEs by preferred term most commonly reported were injection site pain (0.3%) and lymphadenopathy (0.3%) in the aQIV group (vs 0.1% and 0.1% in QIV) and vertigo (0.3%) in the QIV group (vs 0.1% in aQIV). A slight imbalance in the event of lymphadenopathy considered as related to the study vaccine between the groups (3 events in aQIV vs 1 event in QIV) is observed. The MAH accepted the inclusion of Lymphadenopathy.

The rest of related unsolicited AEs were reported from 1 subject only in each vaccine group.

Serious adverse event/deaths/other significant events

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.

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 hospitalized) 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).

During all study period (Day 271) no new safety concern was identified. Only one death assessed as not related in aQIV, due to a lung adenocarcinoma was reported. The frequencies of SAE were low in both groups (3.0% in aQIV and 3.1% in QIV) and none was considered as related to the study vaccine by the investigator or promotor. In addition, there were only 2 subjects who reported AESIs in aQIV; one case of rheumatoid arthritis and one of autoimmune thyroiditis, both considered as not related by the investigator and the promotor.

Laboratory findings

No safety-related clinical laboratory data were collected in Study V118_23.

Safety by subgroups

Safety in special populations

Pregnancy and lactation

Effects of aQIV in pregnancy and lactation have not been studied in Study V118_23 since pregnancy was an exclusion criterion and no pregnancies were reported during the study.

Intrinsic factors

Intrinsic factors for which safety was assessed include age cohort, gender, race, ethnicity, and comorbidity risk score (<50 and ≥50).

By age

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%).

By gender

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

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

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

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

Extrinsic factor for which safety was assessed include previous influenza vaccination history.

By Previous Vaccination History

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.

As indicated, effects of aQIV in pregnancy and lactation have not been studied in Study V118_23 since pregnancy was an exclusion criteria and no pregnancies were reported during the study.

In addition, safety assessment included age cohort (50-59 and 60-64 yoa), gender (male and female), race (White and Black or African American), ethnicity (Hispanic or Latino ethnicity and Not Hispanic or Latino), comorbidity risk score (<50 and ≥50) and previous vaccination history (subjects who had received an influenza vaccination in the previous 3 influenza seasons compared with subjects who had not). However, in the assessment by race and ethnicity, it is not possible to make a conclusion because numbers of participants in Black or African American subgroup (69 subjects) and in Hispanic or Latino ethnicity (25 subjects) are small.

The incidence of SAE and AESIs was low in the overall population. Nonetheless the safety analysis of SAEs or AESIs by subgroups has not been provided. The MAH reported no notable differences in the percentages of SAEs between the aQIV and QIV groups by age, gender, comorbidity risk score, and influenza vaccination history.

Regarding the reactogenicity profile, some difference was observed by subgroups analysis:

- Solicited local and systemic AEs were reported in a higher frequency in participants aged 50-59 than in those 60-64 years. No difference in unsolicited AEs was observed.

- Solicited local and systemic AEs were reported in a higher frequency in female than in male. No difference in unsolicited AEs was observed.

- Solicited local AEs were reported with a higher frequency in subjects who had received an influenza vaccination in the 3 previous influenza seasons compared to subjects who had not. No difference in solicited systemic and unsolicited AEs was observed.

- No difference in frequencies of solicited local and systemic AEs was observed by comorbidity risk score. However, higher incidence of unsolicited AEs was reported in subjects with a comorbidity risk score ≥50 than in subjects with a comorbidity risk score <50.

Safety related to drug-drug interactions and other interactions

Study V118_23 was not designed to prospectively investigate interactions with concomitant vaccinations of medications.

Discontinuation due to adverse events

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.

Post marketing experience

The first approval for marketing worldwide was received in Australia on 24 Sep 2019. aQIV is currently authorized in 38 countries for active immunization against influenza in persons 65 years of age and older.

Analysis of the post-marketing data received for aQIV cumulatively revealed no safety issues. The benefit-risk profile of aQIV is favourable in the approved indication.

2.5.1. Discussion on clinical safety

The aim of this variation was the registration of aQIV for use in persons 50 years of age and older based on the data generated in clinical study V118_23.

The Overall Safety Set for the study V118_23 was 2043 participants aged 50-64 years of age. Of these, 1027 participants received aQIV and 1016 participants received QIV.

The demographic and baseline characteristics were generally comparable between vaccines. However, there were enrolled more female subjects (61.2%) than male subjects (38.8%) and more subjects in the range age 50-59years (59.0%) than in 60-64 years (41.0%). It is known that age and sex could affect the reactogenicity profile in vaccines. Nevertheless, the same percentage of male/female and younger/older was observed in both groups, therefore the possible contribution of baseline characteristics to the reactogenicity profile would be similar in both groups.

In addition, the majority of subjects had a comorbidity risk score <50 (89.6%), suggesting a lower probability of hospitalization due to pneumonia or influenza or death. A high percentage of participants (88.4%) reported at least 1 medical disorder as medical history. Hypertension was the most frequently reported medical history condition (40.1%); all other medical history conditions occurred at a frequency of less than 15%.

Solicited AEs

The number of participants evaluated for solicited AEs was 2028 subjects (1020 subjects in aQIV group and 1008 subjects in QIV group).

Any Solicited AEs were reported by 65.9% vs 53.7% of the evaluated participants, within the first 7 days aQIV or QIV treatment, respectively.

The percentage of subjects reporting solicited local AEs tended to be higher in the aQIV group than the QIV group (49.8% vs 30.4%). The most frequently reported solicited local was injection site pain (47.1% vs 28.1%), followed by induration (7.9% vs 3.5%) and erythema (7.8% vs 3.1%). The majority of solicited local AEs reported were mild or moderate in severity being reported on Day 1 or Day 2. In addition, most of solicited local AEs reported were observed in ≤3 days.

Incidence of each severe solicited local AEs was very low, the highest frequency was 0.4% for erythema in aQIV (vs 0% in QIV) and 0.3% for pain in QIV (vs 0.1% in aQIV).

The percentage of subjects reporting solicited systemic AEs were similar between aQIV group and QIV group (45.3% vs 40.0%). The most frequently solicited systemic AEs in both aQIV and QIV groups were fatigue (29.5% vs 24.3%, respectively) and headache (22.2% vs 20.4%), followed by myalgia (13.0% vs 7.2%) and arthralgia (13.7% vs 9.4%). Fever (≥38.0° C) was reported with low frequency in both aQIV and QIV groups respectively (2.5% and 1.7%). The majority of solicited systemic AEs were mild or moderate in severity with onset most commonly reported on Day 1 or Day 2. In both vaccine groups, most of solicited systemic AEs were observed in ≤3 days.

The frequency of severe solicited systemic AEs was 2.2% in both vaccine groups. Additionally, severe fever (≥39.0^{0}C) was reported by 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.

Unsolicited AEs

Unsolicited AEs within 21 days after vaccination were reported with low and similar frequencies in aQIV and QIV. Specifically, the unsolicited AEs were reported by 16.5% in aQIV and 16.9% in QIV, being the related unsolicited AEs observed in 3.2% and 3.1% respectively. The majority of AEs were assessed as mild or moderate in severity in both vaccine groups. Few subjects reported severe AEs (0.2% vs 0.7%), but data of incidence of severe unsolicited AEs considered as related to the study vaccine are lacking. The MAH was requested to provide this information. The MAH has reported that only one severe event until 28 days after the QIV administration was considered related and no case in the aQIV group.

The related unsolicited AEs by preferred term most commonly reported were injection site pain (0.3%) and lymphadenopathy (0.3%) in the aQIV group (vs 0.1% and 0.1% in QIV) and vertigo (0.3%) in the QIV group (vs 0.1% in aQIV). A slight imbalance in the event of lymphadenopathy considered as related to the study vaccine between the groups (3 events in aQIV vs 1 events in QIV) is observed. The inclusion of Lymphadenopathy under the uncommon frequency category was agreed.

The rest of related unsolicited AEs were reported from 1 subject only in each vaccine group.

Deaths, SAEs and AESIs

During all study period (Day 271) no new safety concern was identified. Only one death assessed as not related in aQIV, due to a lung adenocarcinoma was reported. The frequencies of SAE were low in both groups (3.0% in aQIV and 3.1% in QIV) and none was considered as related to the study vaccine by the investigator or promotor. In addition, there were only 2 subjects who reported AESIs in aQIV; one case of rheumatoid arthritis and one of autoimmune thyroiditis, both considered as not related by the investigator and the promotor.

Safety by subgroups

Effects of aQIV in pregnancy and lactation have not been studied in Study V118_23 since pregnancy was an exclusion criteria and no pregnancies were reported during the study.

In addition, safety assessment included age cohort (50-59 and 60-64 yoa), gender (male and female), race (White and Black or African American), ethnicity (Hispanic or Latino ethnicity and Not Hispanic or Latino), comorbidity risk score (<50 and ≥50) and previous vaccination history (subjects who had received an influenza vaccination in the previous 3 influenza seasons compared with subjects who had not). However, in the assessment by race and ethnicity, it is not possible to make a conclusion because numbers of participants in Black or African American subgroup (69 subjects) and in Hispanic or Latino ethnicity (25 subjects) are small.

The incidence of SAE and AESIs was low in the overall population. Nonetheless the safety analysis of SAEs or AESIs by subgroups has not been provided. The MAH was requested to provide these data by age, gender, comorbidity risk score and previous vaccination history. The MAH has reported that no notable differences were found in the percentages of subjects reporting SAEs between the aQIV and QIV groups by age, gender, comorbidity risk score, and influenza vaccination history.

Regarding the reactogenicity profile, some difference was observed by subgroups analysis:

- Solicited local and systemic AEs were reported in a higher frequency in participants aged 50-59 than in those 60-64 years. No difference in unsolicited AEs was observed.

- Solicited local and systemic AEs were reported in a higher frequency in female than in male. No difference in unsolicited AEs was observed.

- Solicited local AEs were reported with a higher frequency in subjects who had received an influenza vaccination in the 3 previous influenza seasons compared to subjects who had not. No difference in solicited systemic and unsolicited AEs was observed.

- No difference in frequencies of solicited local and systemic AEs was observed by comorbidity risk score. However, higher incidence of unsolicited AEs was reported in subjects with a comorbidity risk score ≥50 than in subjects with a comorbidity risk score <50.

Post marketing experience

The first approval for marketing worldwide was received in Australia on 24 Sep 2019. aQIV is currently authorized in 38 countries for active immunization against influenza in persons 65 years of age and older.

Analysis of the post-marketing data received for aQIV cumulatively revealed no safety issues. The benefit-risk profile of aQIV is favourable in the approved indication.

2.5.2. Conclusions on clinical safety

The aQIV vaccine is well tolerated in subject aged 50-64 years. The incidence of solicited local AEs was higher in aQIV compared to QIV and no difference was observed regarding solicited systemic and unsolicited AEs between two groups. The higher incidence of solicited local AES was mainly driven by differences in site injection pain (47.1% vs 28.1%.) and this not considered a relevant safety issue. The majority of adverse events was mild or moderate in severity and resolved in few days. The incidence of SAEs and AESIs was low in both groups and none was considered related to the study vaccine by the promotor or investigator. No new safety concern was identified.

In addition, in aQIV group, higher reactogenicity was observed in participants aged 50-59 than in those 60-64 years and in female than male subjects.

In conclusion, the safety profile of aQIV is considered to be adequate to support the indication for prophylaxis of influenza in subjects ≥50 years of age.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/ an updated RMP version with this application.

The MAH submitted an updated RMP version. Version agreed is 3.0, DLP = 15 March 2023, sign off date = 02 November 2023). The (main) proposed RMP changes are the following:

Part	**Change**
Part I:	Updated the product overview table with the extension of indication of aQIV from 'prophylaxis of influenza in the elderly (65 years of age and older)' to 'prophylaxis of influenza in adults 50 years of age and older information on booster dose'

Part II SI:	Updated the epidemiology data to reflect the latest information with new reference and added new data on epidemiology, morbidity and mortality data in adults 50-64 years old
Part II SIII:	Latest clinical trial exposure data added (DLP 15 Mar 2023) from studies V200_10 and V118_23
Part II SV:	Latest cumulative post-marketing exposure data added (DLP 15 Mar 2023)
Part II SVII:	There are no important identified risks or important potential risks for aTIV and aQIV.
Part III:	Additional PV activities not required by regulators and summary table of additional pharmacovigilance activities – to remove integrated dataset analysis, a non-interventional study of vaccine effectiveness in US: aTIV/aQIV vaccination vs no vaccination in elderly ≥ 65 years
Part VI:	Updated to reflect extension of indication
Annexes	Annex 2: Updated objectives for completed studies for aTIV and aQIV: V118_20 (2017/2018 USA), V118_18 (2016 – 2018), V200_10 (2020/2021), V118_23 (2021/2022) Updated planned studies for aTIV and aQIV: To remove integrated dataset analysis, To update objectives of study V118_24
	Annex 3: Updated to include the recent version of protocols
	Annex 7: updated to included reference for other supporting data (including referenced material)
	Annex 8: Aligned as per changes in RMP

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.0

2.7. Update of the Product information

The CHMP adopted a change to the existing indication as follows:

Prophylaxis of influenza in **adults** ~~the elderly (65~~ **50** years of age and older~~)~~.

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

Some editorial PI adjustments were carried out.

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

2.7.1. User consultation

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

Adjuvanted Quadrivalent Influenza Vaccine (aQIV; Fluad Tetra/Quad/Quadrivalent) is an egg-derived inactivated subunit quadrivalent influenza virus vaccine adjuvanted with MF59C.1 (MF59), a squalene-based oil-in-water emulsion. Fluad Tetra/Quad/Quadrivalent is licensed in 38 countries (Australia, the United States [US], the European Union [EU] plus Iceland, Norway, and Liechtenstein, New Zealand, United Kingdom, Argentina, Brazil, Republic of Korea, and Taiwan) for use in adults aged 65 years and over.

To support registration of aQIV for use in persons 50 years of age and older, the MAH provides the results on the benefits and risks of aQIV for prevention of influenza in persons 50 to 64 years of age based on the data generated in clinical study V118_23.

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).

Type A viruses are associated with both annual epidemics and pandemics, and B viruses contribute to annual epidemics. The type A viruses are further divided into different subtypes, of which the A/H3N2 and A/H1N1 viruses are the most clinically relevant for 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.

Influenza is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, non-productive cough, sore throat, and rhinitis 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).

3.1.2. Available therapies and unmet medical need

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.

For adults over the age of 50 years, the ability to respond well to vaccination is affected by immunosenescence, in which advancing age diminishes the effectiveness of the immune system. Immune responses against conventional trivalent influenza vaccines in adults ≥58 years of age have been shown to be 10% to 23% lower than in adults younger than 58 years of age.

While it is well established that adults 65 years and older are at greater risk of serious complications from influenza compared with young, healthy adults, there is growing recognition of a high burden of disease in adults aged 50 to 64 years of age.

In the EU, approximately 93 million people are between the age of 50 to 64 years. The impact of seasonal influenza on hospitalizations and mortality was evaluated for 10 influenza seasons between 1996 and 2006 in five European countries (Netherlands, United Kingdom, France, Portugal, and Spain). For hospitalizations, 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%. For deaths, the percentage of all-cause mortality caused by influenza activity in the 50 to 64 years age group was between 1.7% and 3.4%, lower than the 3.2% and 7.4% range observed in the age group 65 years and older. 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. These data indicate influenza disease contributes to a substantial health burden in the 50 to 64-year-old population.

In the US, the estimated rate of hospitalizations 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 (155.1 vs 48.4 per 100,000 population). Furthermore, the estimated number of medical visits due to influenza illnesses is higher in the 50 to 64 years age group (3.97 million) compared with older adults (1.72 million).

In recognition of the high burden of influenza disease in adults 50 to 64 years of age, the US Advisory Committee on Immunization Practices (ACIP) has defined the risk group for older adults as persons aged 50 years and older. In the EU, seasonal influenza vaccine is also recommended for older adults with age of recommendation ranging from ≥50 to ≥65 years (European Vaccination Information Portal, 2022).

Given increased susceptibility to infectious diseases with aging, novel vaccine formulations are needed to elicit effective immunity in older individuals. One way to increase the immunogenicity of influenza vaccines is by using adjuvants. The mechanism of action of the adjuvant MF59 has been extensively detailed in the initial dossier. The immune-enhancing benefit of the adjuvant MF59 in aQIV has been demonstrated in persons 65 years of age and older and its effect is described for persons 50 years and older in the current application.

It is noted that for the age group 50 to 64 YOA, there are other two influenza quadrivalent vaccines approved by the centralized procedure in the EU (Flucelvax Tetra – Sequirus Netherlands, B.V- and Supemtek –Sanofi Paster-). Flucelvax Tetra contains antigens derived from influenza virus grown in cell culture, and is indicated for subjects from 2 yoa. Supemtek is a vaccine containing recombinant HA produced in insect cells, and is indicated for subjects 18 yoa. Moreover, there are also a number of quadrivalent vaccines approved in different EU countries by RMP/DCP procedures (e.g., Mylan IRE Healthcare Limited, Glaxo Smith Kline, S.A., and Sanofi Pasteur Europe, MSD). These vaccines contain viral antigens derived from influenza virus grown in eggs, and have an indication for subjects >= 6 months of age. Thus, there are a number of quadrivalent influenza vaccines available in the EU for subjects 50 to 64 y and thus there is not an unmet medical need for this population. Nonetheless, if this variation procedure were approved, aQIV would represent, for subjects 50-64 yoa, an adjuvanted alternative to current licensed non-adjuvanted vaccines.

3.1.3. Main clinical studies

Study V118_23 was a randomized, comparator-controlled, observer-blind, multicenter study to evaluate the immunogenicity and safety of aQIV versus a licensed non-adjuvanted QIV comparator (QIV) in subjects 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.

A total of 2018 subjects were planned to be enrolled in the study. Subjects 50 to 64 years of age were randomized in a 1:1 ratio to receive aQIV or the QIV comparator vaccine (Fluarix Tetra/Quadrivalent). Randomization was stratified by age (50 to ≤59 years; 60 to ≤64 years) and history of any influenza vaccination within the previous 3 influenza seasons (yes/no). Subjects received a single 0.5 mL dose of vaccine (aQIV or QIV) on Day 1, administered intramuscularly.

The aim of this study was to demonstrate both a noninferior immune response as assessed by geometric mean titre (GMT) ratio and seroconversion rate (SCR) difference for each strain and a superior immune response as assessed by GMT ratio for at least 2 of the 4 strains of aQIV compared with a licensed nonadjuvanted inactivated quadrivalent influenza vaccine (QIV), 3 weeks after vaccination, in adults 50-64 years of age. In addition, immunogenicity, antibody persistence, reactogenicity, and safety were assessed. Data from this study supported the licensure of the quadrivalent version of Fluad for the prevention of seasonal influenza in adults 50-64 years of age.

3.2. Favourable effects

The primary endpoint aimed at demonstrating non-inferiority of aQIV compared with a nonadjuvanted QIV was successfully demonstrated in this study population of subjects 50 to 64 years of age. The prespecified success criteria (upper limit [UL] of the 95% confidence interval [CI] for the Day 22 GMT ratio ≤1.5) were met with respect to the GMT ratio (A/H1N1: 0.87; A/H3N2: 0.99; B/Yamagata: 1.01; B/Victoria: 1.07) and SCR difference (UL of the 95% CI for the difference in SCR is ≤10%) (A/H1N1: -0.89%; A/H3N2: 2.52%; B/Yamagata: 2.22%; B/Victoria: 0.87%; complete serology dataset analysis: A/H1N1: -0.74%; A/H3N2: 2.48%; B/Yamagata: 2.00%; B/Victoria: 0.45%) for all 4 vaccine strains

In relation to the other primary endpoint, 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 hospitalization 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.

New data were presented by the MAH during the assessment procedure. The RCTs compare the immune response of an MF-59 adjuvanted trivalent influenza vaccine vs a non-adjuvanted one, and the results indicate overall a higher immune response of the MF-59 adjuvanted vaccines compared to the non-adjuvanted ones in the age group 50 to 64 yoa. Moreover, evidence from retrospective cohort studies and public health surveillance also indicate adequate vaccine effectiveness of the MF-59 adjuvanted vaccine in the 50-64 and in the 65-74 years age group. This latter age group is the closest one to the sought age

indication of 50 to 64 years. 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 current variation procedure that seeks extending the indication to the 50-64 years age group.

3.3. Uncertainties and limitations about favourable effects

Demonstration of non-inferiority of aQIV vs QIV was clearly demonstrated in terms of SCR differences and GMT titres for all four viral strains. In general, the SCR rates achieved for aQIV were slightly higher for the four viral strains (1.8 to 4.5%) than those achieved when using QIV. Similarly, estimates of GMT titres were always higher for those receiving aQIV than those that received QIV. 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 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. In this sense, the study failed to meet that planned primary objective, and therefore the immunological benefit of aQIV compared to QIV cannot be considered as positive in persons 50 to 64 years of age.

Moreover, even in the case that the results of the "complete serology dataset" were considered relevant, the demonstration of superior immunogenicity for only 2 strains, questions the protection benefit of the vaccine against all four components of the quadrivalent vaccines.

It is unclear how to translate in terms of clinical protection conferred by the vaccine, the higher persistence of antibody response observed 6 months after vaccination to only one strain (A/H1N1) strain.

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 subjects at higher risk of influenza complications due to baseline comorbidities and for subjects 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.

The CHMP guideline on influenza vaccines (EMA/CHMP/VWP/457259/2014) does not specify if superiority needs to be demonstrated for all four influenza strains, but the MAH criterion for success is that superiority needs to be demonstrated in terms of GMTR for at least 2 of the 4 vaccine strains. In order to justify this success criterion, the MAH indicates that the "responses to influenza vaccine strains show high variability across seasons and by strain.... Accordingly, a success criterion of at least 2 of the 4 viral strains being superior to the comparator vaccine represents a clinically meaningful benefit". It is considered that optimally, superiority of aQIv vs QIV in terms of GMT ratio should have been demonstrated for the four viral strains to robustly demonstrate the role of the adjuvant in terms of inducing an increase of the immune response in comparison with a non-adjuvanted vaccine.

The new data regarding RCTs (comparing adjuvanted and non-adjunvanted trivalent vaccines) show overall an immune benefit of the adjuvanted vaccine over the non-adjuvanted one, although this benefit does not translate in statistically superiority (in terms of GMTR) to all vaccine components in every season.

A major weakness of the two retrospective cohort studies that showed higher vaccine effectiveness of the adjuvanted vs non adjuvanted vaccines is that none of them used influenza-confirmed cases as primary effectiveness outcome, which is the preferred endpoint for influenza VE studies.

The public health surveillance study carried out by the United Kingdom Health Security Agency (UKHSA) does not provide relative vaccine effectiveness of an adjuvanted vs a non-adjuvanted vaccine, although 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.

3.4. Unfavourable effects

The safety profile of aQIV in subjects 50-64 years of age was evaluated in the clinical trial V118_23. The overall safety Set included 2043 participants aged 50-64 years (1027 participants received aQIV and 1016 participants received QIV). Solicited AEs were evaluated in the majority of participants (99.3%).

The percentage of subjects reporting solicited local AEs tended to be higher in the aQIV group than in the QIV group (49.8% vs 30.4%), which is mainly explained by the difference regarding injection site pain (47.1% vs 28.1%). However, the percentages of subjects reporting solicited systemic AEs were similar between aQIV group and QIV group (45.3% vs 40.0%).

Most frequently reported solicited AEs were injection site pain (47.1% vs 28.1%), fatigue (29.5% vs 24.3%, respectively) and headache (22.2% vs 20.4%) followed by myalgia (13.0% vs 7.2%) and arthralgia (13.7% vs 9.4%). The majority of solicited AEs (local and systemic) were mild or moderate in severity with onset most commonly reported on Day 1 or Day 2, and were resolved in ≤3 days.

Fever (≥38°C) was reported with low frequency in both groups but slightly higher in aQIV than in QIV (2.5% and 1.7%). Of note, 1 subject, who received aQIV, reported a body temperature of ≥40.0°C.

Unsolicited AEs within 21 days after vaccination were reported with low and similar frequencies in aQIV and QIV. Specifically, the unsolicited AEs considered related were reported by 3.2% and 3.1% respectively. A slight imbalance is observed in the event of lymphadenopathy considered as related to the study vaccine between the groups (3 events in aQIV vs 1 event in QIV). The MAH updated the section 4.8 of the SmPC , including Lymphadenopathy (with frequency uncommon), instead of listing it in the section of adverse reactions reported from post-marketing surveillance.

Deaths, SAEs and AESIs were reported with very low frequencies in both groups and none of the events were considered as related to the study vaccine.

3.5. Uncertainties and limitations about unfavourable effects

The rates of solicited AEs reported through Day 7 after any vaccination were comparable between both vaccine groups (aQIV and QIV) in subjects aged 50-64 years, with the exception of higher local reactions in aQIV than in QIV. The higher incidence of solicited local AES was mainly driven by differences in site injection pain (47.1% vs 28.1%.) and this not considered a relevant safety issue.

Stratifying by age, in participants who received aQIV, higher reactogenicity was observed in subjects aged 50-59 than in those of 60-64 years. However, no comparative analysis between subjects 50-64 years and ≥65 years was performed.

In addition, the overall safety set included 2043 participants aged 50-64 years (1027 participants received aQIV and 1016 participants received QIV). This sample size is sufficient to define the reactogenicity profile; nevertheless, it does not allow to detect adverse reactions of uncommon or rare frequencies.

3.6. Effects Table

Table 28: Effects Table for Fluad Tetra in subjects aged 50-64 years

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
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	aQIV: one dose of a MF-59-adjuvanted quadrivalent vaccine	QIV: one dose of a commercial non-adjuvanted quadrivalent vaccine; Fluarix Tetra (GSK)	GMT Ratio A/H1N1: 0.80 (0.74, **0.87**) Yes A/H3N2: 0.90 (0.82, **0.99**) Yes B/Yamagata: 0.94 (0.88, **1.01**) Yes B/Victoria: 0.99 (0.92, **1.07**) Yes SCR Difference A/H1N1: -4.5 (-8.20, **-0.89**) Yes A/H3N2: -1.8 (-6.12, **2.52**) Yes B/Yamagata: -2.2 (-6.56, **2.22**) Yes B/Victoria: -3.5 (-7.91, **0.87**) Yes	Study V118_23
Primary endpoint 1b	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.	As measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains.	aQIV: one dose of a MF-59-adjuvanted quadrivalent vaccine	QIV: one dose of a commercial non-adjuvanted quadrivalent vaccine; Fluarix Tetra (GSK)	GMT Ratio A/H1N1: 0.80 (0.74, **0.87**) Yes A/H3N2: 0.91 (0.83, **1.002**) No B/Yamagata: 0.95 (0.88, **1.01**) No B/Victoria: 1.00 (0.93, **1.08**) No	Study V118_23
Primary endpoint 1bis	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.	As measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains.	aQIV: one dose of a MF-59-adjuvanted quadrivalent vaccine	QIV: one dose of a commercial non-adjuvanted quadrivalent vaccine; Fluarix Tetra (GSK)	This is a post hoc analysis, with additional serum samples, as compared to primary endpoint 1b. From a methodological and statistical point of view, this analysis can never replace or rescue the main analysis, as there is no free alpha for confirmatory testing GMT Ratio A/H1N1: 0.81 (0.74, **0.88**) Yes A/H3N2: 0.91 (0.83, **0.998**) Yes B/Yamagata: 0.95 (0.88, **1.01**) No B/Victoria: 1.00 (0.93, **1.07**) No	
Unfavourable Effects						
Solicited AEs	aQIV N=1020 QIV N=1008	Incidence rate (%)	65.9% 53.7%			Study V118_23
Solicited local AEs	aQIV N=1020 QIV	Incidence rate (%)	49.8% 30.4%			

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	N=1008					
Solicited systemic AEs	aQIV N=1020 QIV N=1008	Incidence rate (%)	45.3% 40.0%			
Unsolicited AEs within 21 day	aQIV N=1027 QIV N=1016	Incidence rate (%)	16.5% 16.9%			
Usolicited related AEs within 21 days	aQIV N=1027 QIV N=1016	Incidencerate (%)	3.2% 3.1%			
SAEs within 270 days	aQIV N=1027 QIV N=1016	Events (incidence rate)	31 (3.0%) 31 (3.1%)		None related to study vaccine	
AESIS within 270 days	aQIV N=1027 QIV N=1016		2 (0.2%) 0		None related to study vaccine	
Death within 270 days	aQIV N=1027 QIV N=1016		1 (0.1%) 0		None related to study vaccine	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Non-inferiority of aQIV vs QIV in terms of SCR differences and GMT titres was demonstrated for the four influenza viral strains (primary endpoint 1a). However, the primary endpoint 1b that required demonstrating superior response of aQIV in terms of GMT for at least 2 of the influenza viral strains was not met. The additional post-hoc analysis regarding endpoint 1b, that showed superior immune response of aQIV versus QIV for 2 of the 4 vaccine strains (A/H1N1 and A/H3N2), is not considered valid to rescue the first failed analysis from a methodological and statistical point of view.

The new data from three RCTs comparing the immune response of an MF-59 adjuvanted trivalent influenza vaccine vs a nonadjuvanted one, indicate overall a higher immune response of the MF-59 adjuvanted vaccines compared to the non-adjuvanted ones in the age group 50 to 64 yoa. Moreover, evidence from retrospective cohort studies and public health surveillance also indicate adequate vaccine effectiveness of the MF-59 adjuvanted vaccine in the 50-64 and in the 65-74 years age group. This latter age group is the closest one to the sought age indication of 50 to 64 years.

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 approval of the current variation procedure that seeks extending the indication to the 50-64 years age group.

Regarding safety, the aQIV vaccine is well tolerated in subject 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 (47.1 in aQIV %

vs 28.1% in QIV) and this is not considered a relevant safety issue. Thus, from the safety point of view, the extension of the indication to subjects 50 to 64 YOA is supported.

3.7.2. Balance of benefits and risks

Collectively, and despite the limitations commented above, it is concluded that altogether, the evidence provided is sufficient to support approval, from the efficacy point of view, of the current variation procedure that seeks extending the indication to the 50-64 years age group.

The safety data of aQIV do not rise any concern, and therefore the extension of the indication to subjects 50 to 64 YOA is supported.

3.8. Conclusions

The overall B/R of aQIV for prevention of influenza in persons 50 to 64 is positive.

The MAH commits to submit the results of the ongoing study V118_24 to EMA when available.

4. Recommendations

Outcome

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

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

Extension of indication to include adults 50 years of age and older for Fluad Tetra, based on final results from study V118_23; this is a phase 3, randomized, observer-blind, controlled, multicenter, 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. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. Version 3.0 of the RMP has also been approved. In addition, the marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the PI.

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

Amendments to the marketing authorisation

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