19 September 2024
EMA/489437/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of indication variation

Aflunov

Zoonotic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)

Procedure No. EMEA/H/C/002094/II/0086

Marketing authorisation holder (MAH) Seqirus S.r.l

Note

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

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
CI	Confidence Interval
CSR	Clinical Study Report
EMA	European Medicines Agency
FAS	Full Analysis Set
GMR	geometric mean ratio
GMT	geometric mean titre
HA	haemagglutinin
HI	haemagglutinin inhibition
IM	intramuscular
LAR	legally authorised representative
MAA	Marketing Authorisation Application
MF59®	MF59C.1 Adjuvant
MN	microneutralisation
NA	Neuraminidase
NOCD	new onset of chronic disease
PIP	Paediatric Investigational Plan
PPS	Per Protocol Set
SAE	serious adverse event
SC	seroconversion
SRH	Single Radial Haemolysis
US/USA	United States of America
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 S.r.l submitted to the European Medicines Agency on 30 April 2024 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of individuals 6 months of age and older for AFLUNOV, based on final results from study V87_30. This is a Phase 2, Randomized, Observer-Blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Several Doses of Antigen and MF59 Adjuvant Content in a Monovalent H5N1 Pandemic Influenza Vaccine in Healthy Pediatric Subjects 6 Months to < 9 Years of Age. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 5.3 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC.

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

Information on paediatric requirements

Not applicable

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 and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Grazia Evandri Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	30 April 2024
Start of procedure:	27 May 2024
CHMP Rapporteur Assessment Report	25 June 2024
PRAC Rapporteur Assessment Report	25 June 2024
PRAC members comments	3 July 2024
PRAC Outcome	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur Assessment Report	18 July 2024
Request for supplementary information (RSI)	25 July 2024
PRAC Rapporteur Assessment Report	26 August 2024
PRAC members comments	28 August 2024
Updated PRAC Rapporteur Assessment Report	N/A
CHMP Rapporteur Assessment Report	04 September 2024
PRAC Outcome	05 September 2024
CHMP members comments	09 September 2024
Updated CHMP Rapporteur Assessment Report	12 September 2024
Opinion	19 September 2024

2. Scientific discussion

2.1. Introduction

Aflunov is a monovalent influenza avian (zoonotic) vaccine (egg-based, surface antigen, inactivated, MF59C.1 adjuvanted) containing purified Haemagglutinin (HA) and Neuraminidase (NA) surface antigens from the influenza avian virus A/turkey/Turkey/1/2005 (H5N1) like strain (NIBRG-23) clade 2.2.1.

Aflunov 7.5 micrograms HA/0.5 ml dose suspension for injection in pre-filled syringe, was authorised in December 2010. Aflunov approval was based on clinical trials using monovalent MF59C.1 adjuvanted A/H5N1 influenza vaccines including either A/Vietnam/1194/2004(-like) antigen or A/H5N1/turkey/Turkey/1/2005(-like) antigen.

Aflunov is a zoonotic influenza vaccine intended for immunisation in the context of an outbreak of zoonotic influenza viruses with pandemic potential and when there is anticipation of a possible pandemic due to the same or similar influenza strain.

Currently, the approved indication of Aflunov is: "Active immunisation against H5N1 subtype of Influenza A virus. This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of the vaccine containing A/turkey/Turkey/1/2005 (H5N1) like strain (see sections 4.4 and 5.1). AFLUNOV should be used in accordance with official recommendations."

The safety and efficacy of Aflunov in subjects under 18 years of age have not yet been established. Currently available data in subjects aged 6 months to 18 years of age are described in section 5.1 but no recommendation on a posology can be made. No data are available in children aged less than 6 months´.

Seqirus submitted a Type II variation to request an extension of indication in children 6 months of age and above, based on the final results of Study V87_30. The same data package was submitted for Foclivia (EMEA/H/C/00128/II/0081, approved on 17 August 2023). Foclivia is a Seqirus monovalent H5N1 pandemic influenza preparedness pandemic "mock-up" vaccine containing A/Vietnam/1194/2004 strain (surface antigen, inactivated, egg-derived, adjuvanted MF59C.1), 7.5 micrograms HA/0.5 ml dose suspension for injection in pre-filled syringe and in single-dose vial, approved on 18/10/2009. Study V87_30 was conducted to fulfil the commitments in the PIP, EMEA-00599-PIP01-09-M07.

V87_30 study is a dose-ranging study evaluating the safety and immunogenicity of several different formulations using varying amounts of aH5N1 antigen and MF59 adjuvant in paediatric subjects 6 months to less than 9 years of age.

2.1.1. Problem statement

Disease or condition

Zoonotic influenza (a zoonosis) occurs when humans are infected with influenza viruses circulating in animals. Human infections are primarily acquired through direct contact with infected animals or contaminated environments.

Aflunov was developed to protect against a zoonotic influenza viral strain closely matched to strains circulating in avian populations at the time of submission, via early vaccination during pre-pandemic stages (e.g. to reduce mortality in exposed subjects in those countries where infections are occurring). Zoonotic influenza vaccines are intended for active immunisation in the context of an outbreak of zoonotic influenza viruses with pandemic potential, including use in specific groups at high risk of infection from both avian and human viruses like veterinarians or laboratory personnel, and when there is anticipation of a possible pandemic due to the same or similar influenza strain.

Moreover, the zoonotic vaccine may also help reducing the chance of the emergence of a reassortant pandemic strain.

Besides Aflunov, there are currently two other zoonotic influenza vaccines authorised in EU, both from the same marketing authorisation holder (MAH) Seqirus S.r.l.:

-the egg-based "Zoonotic Influenza Vaccine Seqirus" (surface antigen, inactivated, MF59C.1-adjuvanted) based on A/Astrakhan/3212/2020 (H5N8)-like strain (CBER-RG8A) (clade 2.3.4.4b), approved in October 2023 on informed consent by Aflunov, which underwent the strain update from H5N1 to H5N8 in May 2024 (EMEA/H/C/006375/II/0001);

-the cell-based vaccine Celldemic (surface antigen, inactivated, MF59C.1-adjuvanted) based on A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23), approved in April 2024.

State the claimed the therapeutic indication

The claimed therapeutic indication for Aflunov is: Active immunisation against H5N1 subtype of Influenza A virus in persons 6 months of age and above. AFLUNOV should be used in accordance with official recommendations.

The same posology is applied for adult and paediatric subjects:

Individuals 6 months of age and older: administer two doses (0.5 ml each), 21 days apart.

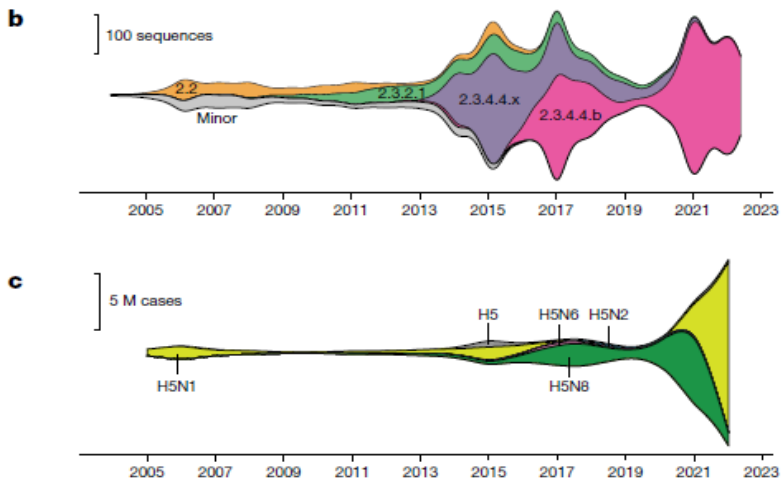
Data on a third dose (booster) administered 6 months after the first dose are limited (see sections 4.8 and 5.1).

No data are available in children aged less than 6 months.

Epidemiology and risk factors, screening tools/prevention

All influenza viruses are genetically labile, that is, likely to change, with mutations occurring from time to time. The constant small changes in the antigenic composition of influenza viruses are known as the antigenic drift. On the other hand, influenza type A viruses, including subtypes from different species, can swap or "re-assort" genetic materials and merge during the re-assortment or mutation process. This phenomenon is known as the antigenic shift. Re-assortment creates optimal conditions for influenza pandemics like the influenza A(H1N1)pdm09 pandemic that occurred in 2009-2010. Three sets of barriers must be crossed by a zoonotic influenza virus before it can become a human pandemic virus: animal-to-human transmission barriers; virus-cell interaction barriers; and human-to-human transmission barriers. Human-to-human transmission barriers are rarely crossed by zoonotic influenza viruses, but these are the events that trigger worldwide influenza outbreaks or pandemics.

As described by Xie R et al. (Nature, 2023) the scale of Highly pathogenic avian influenza (HPAI) H5 outbreaks in wild birds has escalated beyond Asia since 2014, driven by the emergence of H5 HA clade 2.3.4.4 viruses with several NA subtypes including H5N2, H5N6 and H5N8 (collectively H5Nx). From 2016, outbreaks in wild birds were repeatedly caused by clade 2.3.4.4b H5N8 viruses that originated in China. Most recently, a reassortant HPAI H5N1 virus, which evolved from clade 2.3.4.4b viruses, has almost entirely replaced the formerly dominant (from 2014–2021) clade 2.3.4.4b H5N8 viruses (see Figure below). Based on GISAID data, an HPAI virus H5N1 subtype of different clade 2.3.2.1, has been sporadically identified in Asia (https://gisaid.org/phylogeny-influenza/influenza-h5nx/)



From Xie et al., Nature 2023
b, Temporal changes in HPAI H5 HA clade prevalence estimated using sample collection dates of sequences submitted to the GISAID and NCBI Influenza Virus Resource databases from January 2004 to June 2022.
c, Temporal changes in HPAI H5Nx subtype prevalence estimated using observation dates of all reported cases submitted to the WOAH from January 2005 to January 2022.

Since the first detection of zoonotic transmission of HPAI A(H5N1), limited clusters of human cases have occurred, but no sustained human-to-human transmission has been observed. Zoonotic transmission to humans from infected birds occurs either directly or through environmental contamination. The risk for

occupationally or otherwise exposed groups to avian influenza-infected birds or mammals according to the World Health Organization (WHO) is assessed as 'low to moderate'.

Overall, from 2003 to 2023, a total of 878 human cases for avian influenza A(H5N1) were reported to the WHO, with a fatality rate of 52% (Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2023.

With regards to infections due to H5N1 clade 2.3.4.4b viruses, since December 2021, the WHO has reported a few human infections (8): 2 cases, United Kingdom 3 cases, United States 1 case, Vietnam 1 case, Ecuador 1 case, Chile 1 case. The severity of the disease has varied widely from asymptomatic, mild to severe, with fatality. Most patients had exposure to infected poultry, except for the Chilean case; however, highly pathogenic H5 outbreaks were reported in the vicinity of the patient's residency. In July 2023 the European Centre for Disease Prevention and Control (ECDC) stated that, currently, avian influenza virus A(H5Nx) transmission to humans remains a rare event, because despite the high number of exposure events due to the large outbreaks in poultry and wild birds since 2020, no symptomatic human infection due to avian influenza A(H5Nx) has been reported from EU/EEA countries (Public health situation for avian influenza A(H5) viruses https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/avian-influenza/threats-and-outbreaks/situation-ah5). The detection of Influenza A(H5N1) virus in two asymptomatic poultry farm workers in Spain in 2022 was finally classified as suspected environmental contamination. The recent global shift in the ecology of H5N1 HPAI, and avian influenza spillover into mammals (Venkatesan P et al., Lancet Microbe 2023) both raise concerns and prompt pandemic preparedness. Thus, the Food and Agriculture Organization of the United Nations (FAO), the WHO, and the World Organisation for Animal Health (WOAH) urge actions against the ongoing avian influenza outbreaks in animals that continue to pose risk to humans. The acquisition of adaptive mutations in mammals warrants continuous monitoring of H5N1 clade 2.3.4.4b viruses for the presence of mutations that could potentially increase their pandemic risk for humans.

Thus, to strengthen pandemic preparedness activities, a strain update for the "Zoonotic Influenza Vaccine Seqirus" was approved on April 2024 (EMEA/H/C/006375/II/0001). As agreed with the EMA and the ETF, the Candidate Virus Vaccine with the greatest potential coverage against the avian viruses of concern which are currently of clade 2.3.4.4b, would be based on antigenic prototype strain A/Astrakhan/3212/2020 (H5N8). The Candidate Virus Vaccine identified was CBER-RG8A A/Astrakhan/3212/2020 (clade 2.3.4.4b).

Biologic features-aetiology and pathogenesis

Influenza viruses are classified into types A, B and C on the basis of their core proteins. Of the three types of influenza viruses, A and B are associated with significant seasonal morbidity and mortality. Moreover, type A viruses can cause influenza in humans as well as in animals such as poultry, pigs and horses which is particularly relevant to public health. Transmission of influenza A between animals and humans that can potentially contribute to the emergence of a pandemic.

Type A viruses are further subdivided according to their envelope glycoproteins with haemagglutinin (HA) or neuraminidase (NA) activity. There are 18 different HA subtypes and 11 different NA subtypes.

Most subtypes of influenza A viruses have been found in birds, with the exception of subtypes A(H17N10) and A(H18N11) which have only been found in bats. Depending on the original animal host, influenza type A viruses can be classified as avian influenza or swine influenza and include other types of zoonotic influenza viruses.

Examples of zoonotic influenza include avian influenza, also known as "bird flu", with virus subtypes A(H5N1) and A(H9N2), and swine influenza, also known as "swine flu", with virus subtypes A(H1N1) and A(H3N2).

The virus is transmitted primarily by droplets or respiratory secretions of infected patients. The virus binds to and enters the tracheobronchial ciliated epithelium by utilising the viral surface haemagglutinin. Viral replication then occurs. Peak viral shedding occurs in the first 48 to 72 hours of exposure to the virus, then declines and becomes undetectable within 10 days.

Children and immunocompromised people may shed virus for several weeks.

Clinical presentation, diagnosis

Influenza is an acute respiratory disease which is characterized by a sudden onset of high fever, coryza, cough, headache, prostration, malaise, and inflammation of the upper respiratory tract. In the majority of cases, pneumonic involvement is not clinically prominent. Acute symptoms and fever often persist for 7 to 10 days. Weakness and fatigue may linger for weeks.

Immunocompromised individuals, people with diabetes mellitus or chronic pulmonary or cardiac disease, are at high risk of developing severe complications from influenza A viruses.

Severe complications can consist of haemorrhagic bronchitis, pneumonia (primary viral or secondary bacterial), and death. Haemorrhagic bronchitis and pneumonia can develop within hours. Fulminant fatal influenza viral pneumonia occasionally occurs; dyspnoea, cyanosis, haemoptysis, pulmonary oedema, and death may proceed in as little as 48 hours after the onset of symptoms.

Management

In the event of a zoonotic influenza, vaccines are the most effective means of preventing and controlling the spread of virus amongst the human population.

There is no universal vaccine against zoonotic influenza. The major challenge to developing broadly effective vaccines against zoonotic influenza is that within subtypes there are hundreds of strains that may vary slightly, and which naturally and frequently mutate to create new strains.

Aflunov is a specific vaccine against the particular subtypes influenza A(H5N1).

2.1.2. About the product

Aflunov is a monovalent influenza avian (zoonotic) vaccine (egg-based, surface antigen, inactivated, MF59C.1 adjuvanted) containing purified HA and NA surface antigens from the influenza avian virus A/turkey/Turkey/1/2005 (H5N1) like strain (NIBRG-23) clade 2.2.1.

The approved indication was:

Active immunisation against H5N1 subtype of Influenza A virus.

This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of the vaccine containing A/turkey/Turkey/1/2005 (H5N1) like strain (see sections 4.4 and 5.1). AFLUNOV should be used in accordance with official recommendations.

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

The purpose of this study V87_30 was to provide additional clinical data on a paediatric aH5N1 dose in anticipation of an avian influenza pandemic, as agreed in the PIP with the EMA/Paediatric Committee Compliance with CHMP guidance.

The most relevant CHMP guidelines applied is: "Guideline on Influenza vaccines; Non-clinical and Clinical Module" (CPMP/VWP/457259/2014).

2.1.4. General comments on compliance with GCP

The clinical trial V87_30 was conducted in sites located in Estonia (2 centres) and outside the European Union in the Philippines (5 centres). One site in Estonia was inspected by Estonian competent authority on January 2021. The date of study initiation is 19 December 2020, and the date of study completion is 15 April 2022.

The MAH states that the trial was conducted in accordance with Good Clinical Practice (GCP) in line with the International Conference on Harmonization (ICH) guidelines as well as national regulatory requirements, which cover ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical study

Study Identifier; Number of Study Centres, Location (s)	Study Design (Phase, Randomized, Control Type, Blinding)	Study Objectives	Test Vaccine(s); Number of Vaccinations; Route of Administration; Dose and Amount MF59	Health or Diagnosis; Age Population; Number of Subjects per Arm (Enrolled Population)[a]; Mean Age (Range)[b]; Gender (M/F)[b];	Study Dates; Link to Report
V87_30 2 centres in Estonia and 5 centres in the Philippines	Phase 2 Randomised, observer-blind, dose-ranging	Immunogenicity, dose selection and safety	MF59 adjuvanted, inactivated monovalent, A/turkey/Turkey/1/2005 strain (H5N1) vaccine Two vaccinations, 3 weeks apart Subjects were stratified by site and age (6 months to <36 months and 3 years to <9 years) and randomized equally into 6 dosing groups 0.25-0.5 mL IM Doses (0.25 mL) contained: 1.875, 3.75, or 7.5 HA with 0.125 mL MF59 Doses (0.5 mL) contained: 1.875, 3.75, or 7.5 HA with 0.25 mL MF59	Healthy paediatric subjects 6 months to <9 years of age TOTAL N: 420 1.875 µg + 0.125 mL[c]: 69 3.75 µg + 0.125 mL: 72 7.5 µg + 0.125 mL 70 1.875 µg + 0.25 mL: 70 3.75 µg + 0.25 mL: 69 7.5 µg + 0.25 mL 70 49.3 (7; 107) months 228 M/192 F	Dec-2020 Apr-2022 V87_30 CSR V87_30 CSR Addendum V87_30 Synopsis
Source: CSR V87_30 Abbreviations: CSR = Clinical Study Report; HA = hemagglutinin; F = female; IM = intramuscular; M = male. [a] Enrolled as randomised. For safety parameters subjects were analysed as treated. [b] Based on the All Enrolled set. [c] MF59 volume.					

2.4. Clinical efficacy

2.4.1. Main study(ies)

Study Number: V87_30

Study Title: A Phase 2, Randomized, Observer-Blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Several Doses of Antigen and MF59 Adjuvant Content in a Monovalent H5N1 Pandemic Influenza Vaccine in Healthy Paediatric Subjects 6 Months to < 9 Years of Age.

Methods

Eligible subjects were stratified by age at the time of enrolment into one of two age cohorts: 6 months to <36 months of age and 3 years to <9 years of age.

Within each age cohort, subjects were randomly assigned (1:1:1:1:1:1) to 1 of 6 vaccine groups.

Subjects in each vaccine group were scheduled to receive 2 injections of the assigned aH5N1 vaccine formulation 3 weeks apart.

In this study, the 5 vaccine formulations with decreased content of HA antigen and/or MF59 adjuvant (Arms A to E in Table 1) were evaluated together with the formulation containing the licensed dosage for adults of 7.5 µg H5N1 HA antigen in combination with 0.25 mL (100%) MF59 (Arm F in Table 1).

Table 1: H5N1 HA and MF59 Content of the 6 Vaccine Formulations

Arm	H5N1 HA Antigen Dose	MF59 Content	Injection Volume
A	1.875 µg	0.125 mL (50% MF59)	0.25 mL
B	3.75 µg	0.125 mL (50% MF59)	0.25 mL
C	7.5 µg	0.125 mL (50% MF59)	0.25 mL
D	1.875 µg	0.25 mL (100% MF59)	0.5 mL
E	3.75 µg	0.25 mL (100% MF59)	0.5 mL
F	7.5 µg	0.25 mL (100% MF59)	0.5 mL

Abbreviations: HA = hemagglutinin.

Note 1: The currently licensed adult formulation for aH5N1 is 7.5 µg HA of H5N1 influenza strain combined with 0.25 mL MF59 in a total injection volume of 0.5 mL (ie, the vaccine formulation received by subjects in Arm F).

Immunogenicity was measured by HI and MN assays. Blood samples for serology assessments were collected from each subject on Day 1 (before randomization), Day 22 (before vaccination), Day 43, and Day 202 for primary immunogenicity objective evaluation and at Day 202 (6 months after the second vaccination for secondary immunogenicity objective evaluation.

A total of 420 subjects were projected for enrolment and each participant was to be followed for a period of 12 months after receipt of the second dose of study vaccine.

This was a Phase 2, randomized, observer-blind, multicenter study to evaluate the immunogenicity and safety of several doses of antigen and MF59 adjuvant content in a monovalent H5N1 Pandemic Influenza vaccine in healthy paediatric subjects 6 Months to <9 years of age. The two age cohorts were randomized into: 6-36 months and 3 <9 years of age, which was considered acceptable and in line with the relevant GL on influenza vaccines nonclinical and clinical modules (EMA/CHMP/VWP/457259/2014); the inclusion of the younger age group to ensure adequate representation of subjects who were most likely to be naive to influenza and therefore allowing for the assessment of the ability of the first dose to prime, moreover randomization into age cohorts took into account the possible age effect.

The study design is considered adequate and compliant with GL EMA/CHMP/VWP/457259/2014. Results would provide data on the chosen dose, schedule and support the selection of the antigen-adjuvant ratio.

Study participants

Inclusion criteria

- Paediatric subjects in good health as determined by medical history, physical assessments, and clinical judgment. All the inclusion criteria described below needed to be meet:

1. Healthy male and female subjects of 6 months through <9 years of age on the day of informed consent/assent.

2. Documented consent provided by the subject's parent(s)/LAR(s) had voluntarily given written informed consent/assent after the study had been explained according to local regulatory requirements.

3. Subject's parent(s)/LAR(s) able to comprehend and comply with all study procedures, and available for all clinic visits and telephone contacts scheduled in the study.

4.Subjects must provide a baseline blood sample within 10 days prior to the Day 1 vaccination.

Exclusion criteria (subjects were not allowed to meet any of them)

1. Progressive, unstable or uncontrolled clinical conditions.

2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment used in this study.

3. Clinical conditions representing a contraindication to IM vaccination and blood draws, i.e, a. Subjects who had a fever (body temperature measurement ≥38°C) within 3 days prior to vaccination. The subject could return for vaccination after they had been free of fever for 3 days b. History of epilepsy or convulsions (excluding febrile convulsions). c. A subject who had any medical condition meeting the definition of AESI defined for the purposes of this trial. d. Subjects who had received antipyretic medication within the past 24 hours prior to vaccination. The subject could return for vaccination after a period of 24 hours had passed since the administration of an antipyretic

4. Abnormal function of the immune system resulting from: a. Clinical conditions. b. Systemic administration of corticosteroids (PO/IV/IM)1 for more than 14 consecutive days within 90 days prior to informed consent/assent. Topical, inhaled and intranasal corticosteroids were permitted. Intermittent use (one dose in 30 days) of intra-articular corticosteroids was also permitted. c. Administration of antineoplastic and immunomodulating agents or radiotherapy from within 90 days prior to informed consent/assent.

5. Suspicion of pandemic influenza illness within past 6 months or had ever received previous pandemic H5N1 flu vaccination.

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

7. Received an investigational or non-registered medicinal within 30 days prior to informed consent/assent.

8. Children of study site staff (including research or clinic staff) or children who were otherwise related to study site staff or had household members who were study site staff.

9. Any other clinical condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.

10. Individuals who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrolment in this study or who were planning to receive any vaccine prior to Day 43. Following Day 43, other vaccines could be administered, including seasonal flu.

Prior to receipt of the second vaccination, subjects had to be re-evaluated to confirm that they were eligible for subsequent vaccination. If subjects met any of the original exclusion criteria listed above, they were not to receive the second vaccination. These subjects would be requested to fulfil all the scheduled clinic visits and calls for safety follow-up.

Subjects enrolled in the study were healthy male and female subjects 6 months through <9 years of age.

Exclusion of subjects with pandemic influenza illness within past 6 months or ever having received previous pandemic H5N1 flu vaccination or who were administered with other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrolment in this study or who were planning to receive any vaccine prior to Day 43 is acknowledged.

Overall inclusion and exclusion criteria are considered adequate to address the aim of the study and to describe the target population of healthy subjects naïve to influenza virus.

In a pandemic situation, children may be very vulnerable to infection and so constitute a special target group for vaccination.

Treatments

Investigational Vaccine: aH5N1. Six different formulations of the aH5N1 vaccine based on combinations of 3 amounts of H5N1 HA (1.875 µg, 3.75 µg, 7.5 µg) and 2 MF59 dosages (0.125 mL [50%], 0.25 mL [100%]) were tested. In Arm F the currently licensed adult formulation for aH5N1 (7.5 µg HA of H5N1 influenza strain combined with 0.25 mL MF59) is reported.

Table 2: H5N1 HA and MF59 content of the 6 vaccine formulations

Arm*	H5N1 HA content	MF59 content**	Injection volume
A	1.875 µg	50% MF59	0.25 mL
B	3.75 µg	50% MF59	0.25 mL
C	7.5 µg	50% MF59	0.25 mL
D	1.875 µg	100% MF59	0.5 mL
E	3.75 µg	100% MF59	0.5 mL
F	7.5 µg	100% MF59	0.5 mL

*Approximately 70 subjects will be randomized per treatment arm, ie, 35 subjects in each age cohort.
**50% MF59 refers to half the standard MF59 content of the licensed adult formulation for H5N1.

Table 3: Full composition of the active vaccine components

Composition of the active vaccine components	
Component	7.5 µg + 100% MF59 per 0.5 mL
Influenza virus surface antigens (HA and NA) A/turkey/Turkey/1/2005 (H5Nl)-like (NIBRG-23)	~ 7.5-µg HA
% MF59 content relative to commercial vaccine	100%
Squalene	9.75 mg
Polysorbate 80	1.175 mg
Sorbitan trioleate	1.175mg
Sodium citrate dihydrate	0.66mg
Citric acid monohydrate	0.04mg
Sodium chloride	[redacted]
Potassium chloride	[redacted]
Potassium dihydrogen phosphate	[redacted]
Disodium phosphate dihydrate	[redacted]
Magnesium chloride hexahydrate	[redacted]
Calcium chloride dihydrate	[redacted]
Water for injection	Up to 0.5 mL
Vaccine Presentation	Prefilled syringe
Volume of Component	-0.5 mL

The lot numbers of the 6 vaccine formulations evaluated in Arms A to F are shown below:

aH5N1 Vaccine Formulation	Lot Number	Expiry Date
Arm A: 1.875 µg H5N1 HA antigen + 0.125 mL MF59 (0.25 mL PFS)	291527	31 May 2022
Arm B: 3.75 µg H5N1 HA antigen + 0.125 mL MF59 (0.25 mL PFS)	291528	31 May 2022
Arm C: 7.5 µg H5N1 HA antigen + 0.125 mL MF59 (0.25 mL PFS)	291529	31 May 2022
Arm D: 1.875 µg H5N1 HA antigen + 0.25 mL MF59 (0.5 mL PFS)	288470	31 May 2022
Arm E: 3.75 µg H5N1 HA antigen + 0.25 mL MF59 (0.5 mL PFS)	291526	31 May 2022
Arm F: 7.5 µg H5N1 HA antigen + 0.25 mL MF59 (0.5 mL PFS)	288471	31 May 2022

Abbreviations: HA = hemagglutinin; PFS = prefilled syringe.

Within a vaccine group, each eligible subject was to receive 2 vaccinations with the assigned vaccine dose, with the first vaccination on Day 1 and the second vaccination on Day 22.

Criteria for Delay of Vaccination These situations are listed below. If a subject met a criterion for delay of vaccination, the subject was allowed to receive study vaccination once the window for delay had passed as long as the subject was otherwise eligible for study participation.

• Acute moderate or severe infection with or without fever within 3 days of intended study vaccination.

• Fever, defined as body temperature ≥38.0°C (100.4°F) within 3 days of intended study vaccination.

• Administration of any vaccine not foreseen by the study protocol within 7 days prior to intended study vaccination.

There could be instances when individuals met all eligibility criteria for vaccination yet had a transient clinical circumstance which could warrant delay of vaccination: body temperature elevation (≥38.0°C [100.4°F] within 3 days prior to intended study vaccination) or acute use of antipyretics and/or analgesic medications within 24 hours prior to vaccination. Under such circumstances, a subject was considered eligible for study enrolment or next study vaccination after the appropriate window for delay had passed and inclusion/exclusion criteria had been rechecked, and if the subject was confirmed to be eligible.

Non-Study Vaccines

The term 'non-study vaccine' refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives. No "non-study vaccine" was given as part of this study.

Subjects were not prohibited from receiving other vaccinations during the course of the trial as long as they were not an influenza vaccination administered prior to visit 3 (Day 43). Following Day 43 other vaccines could have been administered, including seasonal flu.

Six different formulations of the aH5N1 vaccine were tested in this dose-finding study, in details: 5 vaccine formulations with different content of HA antigen and/or MF59 adjuvant (Arms A to E) were evaluated together with the formulation containing the licensed dosage for adults of 7.5 µg H5N1 HA antigen in combination with 0.25 mL (100%) MF59 adjuvant (Arm F).

Criteria for allowing a delay in subsequent study vaccination are set and acceptable. A non-influenza vaccination could be administered prior to D43, this is also acceptable.

Objectives

The purpose of this study was to assess the safety and immunogenicity of 6 vaccine formulations including 1.875 µg, 3.75 µg, or 7.5 µg HA of pandemic H5N1 influenza strain combined with 0.125 mL or 0.25 mL MF59, in 2 intramuscular (IM) injections administered 3 weeks apart.

Outcomes/endpoints

Primary objectives/endpoints: immunogenicity

Primary Immunogenicity Measurement: immunological responses to the different doses of antigen and adjuvant contained in the 6 vaccine formulations of aH5N1 were evaluated using HI and MN assays with egg-derived H5N1 target virus. Blood samples were obtained on Day 1 (prior to the first vaccination), on Day 22 (3 weeks after the first vaccination, prior to the second vaccination), and on Day 43 (3 weeks after the second vaccination). HI and MN antibody titers on Days 22 and 43 were compared with the baseline antibody titers to evaluate immunogenicity.

The primary immunogenicity objective was to assess by total population and by age cohort, the antibody responses to each of the study vaccines prior to (Day 1) and at 3 weeks after the first or second vaccination (Day 22 or Day 43), as measured by HI and MN assays.

The measures of immunogenicity, as determined by the HI and MN assay against the H5N1 pandemic influenza homologous strain included the following:

– Geometric mean titers (GMTs) on Day 1 and Day 22 (3 weeks after the first vaccination) or Day 43 (3 weeks after the second vaccination) as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain

– Geometric mean ratios (GMRs) calculated as follows: Day 22/Day 1 or Day 43/Day 1 as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain

– Percentage of subjects achieving seroconversion (non-detectable to ≥1:40, or 4-fold increase from a detectable Day 1 titer) on Day 22 or 43

– Percentage of subjects achieving seroconversion with a titer ≥1:40 on Days 1, 22 or 43.

All primary immunogenicity endpoints are described by vaccine group for the overall study population and by age cohort (6 months to <36 months; 3 years to <9 years).

The primary safety objective was to evaluate the safety in each study vaccine group from Day 1 through Day 387, by total population and by age cohort.

The measures for assessing safety and reactogenicity were as follows:

– Percentages of subjects with solicited local and systemic AEs that occurred within 7 days following each vaccination and calculated for 4-time intervals after vaccination: 30 minutes, 1 through 3 days, 4 through 7 days, and 1 through 7 days

– Percentages of subjects with any unsolicited AEs reported within 21 days after each vaccination within each vaccine group

– Percentages of subjects reporting serious adverse events (SAEs), new onset of chronic disease (NOCDs), adverse events of special interest (AESIs), and AEs

Safety measurement: the period of observation for AEs extended from the time the subject signed informed consent/assent until he or she completed the specified safety follow-up period Visit 7 (Day 387) or terminated the study early (whichever came first).

Adverse events were collected as either solicited or unsolicited AEs. Solicited AEs were derived from organized data collection systems, such as subject diaries or interview. Solicited Adverse Events: the term "reactogenicity" refers to solicited signs and symptoms ("solicited AE") occurring in the hours and days following a vaccination, to be collected by the subject's parent(s)/LAR(s)/caregiver for 7 consecutive days, using a predefined Subject Diary Card. In this study there were two versions of the Subject Diary Card: one version for children aged <3 years and one version for children aged 3 years and older.

For children 6 months to <36 months of age, solicited local AEs included injection site erythema, injection site induration, injection site ecchymosis, and injection site tenderness; solicited systemic AEs included change in eating habits, shivering, sleepiness, irritability, vomiting, diarrhoea, and body temperature ≥38.0°C. For children 3 years to <9 years of age, solicited local AEs included injection site erythema, injection site induration, injection site ecchymosis, and injection site pain; solicited systemic AEs included loss of appetite, nausea, fatigue, malaise, generalized myalgia, generalized arthralgia, headache, shivering/chills, vomiting, diarrhoea, and body temperature ≥38.0°C.

AESI: subjects were assessed at each clinic visit for any new medical events or signs or symptoms that could possibly indicate an AESI. A diagnosis of an AESI was to be categorized as an SAE and documented on the Adverse Events eCRF within 24 hours of the site becoming aware of an AESI diagnosis.

New Onset of Chronic Disease (NOCD): was defined as an illness that started during the course of the study that did not exist prior to enrolment into the study and was likely to persist throughout the lifetime of the subject. A chronic disease is one that can be treated but for which no cure exists.

There was no primary efficacy objective/endpoint in this study.

Secondary objectives/endpoints

Secondary Immunogenicity Measurement: the persistence of immunological responses to the different doses of antigen and adjuvant contained in the 6 vaccine formulations of aH5N1 was evaluated using HI and MN assays. Blood samples were obtained on Day 1 (prior to the first vaccination) and on Day 202 (6 months after the second vaccination). HI and MN antibody titers on Day 202 were compared with the baseline antibody titers to evaluate persistence of immunogenicity.

The secondary immunogenicity objective was to evaluate in each study vaccine group, by total population and by age cohort, the persistence of antibody responses to the H5N1 vaccine strain 6 months after the second vaccination (Day 202) as measured by HI and MN assays.

The measures of persistence of antibody responses on Day 202 to study vaccine after primary vaccinations, as determined by the HI and MN assays against the H5N1 pandemic influenza homologous strain:

− Geometric mean titers on Day 1 and Day 202 (6 months after the second vaccination) as determined by HI and MN assays

− Geometric mean ratios calculated as follows: Day 202/Day 1 as determined by HI and MN assays

− Percentage of subjects achieving seroconversion (non-detectable to ≥1:40, or 4-fold increase from a detectable Day 1 titer) on Day 202

− Percentage of subjects achieving seroconversion with a titer of ≥1:40 on Day 202

All secondary immunogenicity endpoints were described by vaccine group and by age cohort (6 months to <36 months; 3 years to <9 years).

There was no secondary efficacy objective/endpoint in this study.

Primary and secondary objectives are adequate to the aim of the study and in line with the GL EMA/CHMP/VWP/457259/2014 requirements. Immunogenicity assessment, using HI and MN assays, is comprehensive of the immunological data generated by standard approach such as GMTs with 95% confidence intervals and GMRs, seroconversion rates, persistence, required by regulatory guidelines. Timing of sampling seems adequate to the 2-dose vaccination scheme, however it is of note that for adjuvanted seasonal vaccines follow-up of persistence of response should be investigated up to 12 months after completion of the initial regimen to investigate the need for annual revaccination. However, in the V87_30 study this period is shorter (the last measurement is set at 6 months from second vaccine dose), but this may be reasonable for a vaccine intended for H5N1 response.

Absence of efficacy endpoints is acceptable since it is not expected that clinical efficacy should/can be established at the time of the marketing authorisation.

Exploratory Objectives and Endpoints

The exploratory objective was to further evaluate the antibody responses to seasonal, and/or homologous and/or heterologous pandemic influenza strain(s) by vaccine group on Days 1, 22, 43, and 202, as measured by HI, MN, or single radial hemolysis (SRH) assays (depending on availability of adequate sera and on assay availability).

Sample size

This was a dose-ranging study without inferential hypothesis testing. A total number of 420 subjects were planned to be enrolled in the study. This number of subjects should provide sufficiently accurate estimates of the GMT to evaluate the paediatric dose. Assuming an exclusion rate of up to 14% of subjects from the analysis, around 180 subjects per age cohort would be included in the analysis. With equal allocation to one of 6 vaccine groups, at least 60 subjects were expected per vaccine group and at least 30 subjects per vaccine group and age cohort were expected to be evaluable for the statistical analysis. No formal power calculations were done.

All data was analysed descriptively. Statistical analyses of the immunogenicity endpoints included point estimates and the associated 95% confidence intervals (Cis). However, the accuracy of the estimates of the GMTs can be illustrated by the length of the 95% CIs. Assuming an SD of log10–transformed HI titers as 0.7 (based on studies V87_25 and V87_26 in healthy elderly adults):

• With n=30 per dose group per age cohort, the 95% CI will be from 0.56 to 1.78 times the GMT estimate

• With n=60 per dose group; the 95% CI will be from 0.67 to 1.50 times the GMT estimate

As the decision on objectives does not involve testing procedures, adjustment for multiplicity is not applicable.

Sample size was not based on formal power calculations. The minimum number of subjects expected to be evaluable for statistical analysis was calculated as at least 30 subjects per vaccine group and age cohort to provide a specific width of 95%CI around the GMT estimate based on HI titers from previous studies in adult subjects.

Results are merely descriptive and no pairwise dose-group comparisons are shown.

Randomisation

Subject identification (ID) was manually entered in the electronic data capture (EDC) system. Subject information and stratification information (i.e., age) were automatically transferred to the interactive response technology (IRT) system for randomization in a 1:1:1:1:1:1 ratio into 6 treatment groups and automatically assigned a unique pack ID.

Randomization was stratified by age (cohorts of 6 months to <36 months and 3 years to <9 years) and by site. The age cohorts were planned to be of equal size. Once an age cohort attained its planned size (i.e., half of the planned study sample size), the randomization in this age cohort would be blocked.

The randomization approach and scheme are acceptable. Stratification according to age cohorts is of importance to exclude the age impact on immune response, and, as stated before, inclusion of the younger cohort allows to obtain a population characterized by low/absent pre-existing influenza immunity subjects. Site randomization is also acknowledged.

Blinding (masking)

The study was an observer-blind study.

Vaccine preparation and administration were to be completed by the designated unblinded team members. Any other subject related assessments were to be performed by the PI and/or blinded staff members as applicable. Sponsor personnel, except the Clinical Vaccines Management (CVM) team (which is responsible for labelling, packaging and distribution), were to remain blinded.

Except in the case of medical necessity, a subject's treatment was not to be unblinded without the approval of the Sponsor.

Statistical methods

The analysis of the data from this study was based on the final Statistical Analysis Plan (SAP) Version 1.0 (Final, dated 06 May 2022), which was finalized before unblinding.

In general, summary descriptive statistics of continuous data are presented as number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). For categorical variables, statistical summaries include counts and percentages relative to the appropriate population.

Analyses set

The following analysis populations were defined for the study analyses:

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

All Exposed Set - All subjects in the All Enrolled Set who received at least one dose of study vaccination.

Solicited Safety Set - All subjects in the All Exposed Set with any solicited AE data collected, including temperature measurements or use of analgesics/antipyretics. Subjects with a confirmation of no indicators of solicited AE (for example vomiting is "none" or injection site-induration is 0 mm [none]) were included in this population as well.

Unsolicited Safety Set - All subjects in the All Exposed Set with unsolicited AE data. Subjects with a confirmation of no unsolicited AE were included in this population as well.

Overall Safety Set - All subjects in the Solicited Safety Set and/or the Unsolicited Safety Set. Subjects were analyzed "as treated" (ie, according to the vaccine formulation a subject received, rather than the vaccine formulation to which the subject may have been randomized). Subjects randomized in the wrong age stratum were reassigned to the correct age stratum and analyzed using corrected stratum for all safety sets (i.e, Solicited Safety Set, Unsolicited Safety Set and Overall Safety Set). If a subject was unblinded during the study, he/she was included in all the safety sets.

Full Analysis Set (FAS) Immunogenicity All subjects in the All Enrolled Set who were randomized, received at least one study vaccination, and provided immunogenicity data at any time point. In case of vaccination error, subjects in the FAS sets were analysed "as randomized" (ie, according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

Per Protocol Set (PPS) Immunogenicity All subjects in the FAS immunogenicity who:

• Correctly received the vaccine (i.e, received the vaccine to which the subject was randomized and at the scheduled time points)

• Provided at least the baseline and one postbaseline blood sample, with evaluable immunogenicity data

• Had no protocol deviations leading to exclusion as defined prior to unblinding/analysis.

All immunogenicity analyses (primary, secondary, and exploratory) were performed in the PPS Immunogenicity.

The primary immunogenicity analyses would be also performed in the FAS Immunogenicity if the percentage of subjects excluded from the PPS Immunogenicity was >5%.

All solicited safety analyses were performed in the Solicited Safety Set; all unsolicited safety analyses were performed in the Unsolicited Safety Set.

Demography and baseline characteristics tables as well as subject listings were produced for the All Enrolled Set.

Subgroup Analyses Age cohort (6 months to <36 months and 3 years to <9 years, based on the actual age) was used as a subgroup for all study primary and secondary endpoints. In addition, as described in the SAP descriptive immunogenicity analysis of the GMTs was performed by stratifying for the following subgroups:

- Sex
- Country
- Site

Primary Immunogenicity Endpoint Methodology

Antibody titers below the lower limit of quantification (LLOQ) were set to half that limit (e.g, 5 if the LLOQ is 10). Values above the upper limit of quantification (ULOQ) were set to the value of this upper limit. Missing immunogenicity data were excluded from analysis of the immunogenicity endpoints. Imputation methods were therefore not applied. Sensitivity analyses could be considered to assess the impact of missing data in case of substantial missing data.

Geometric Mean Titer For the evaluation of GMTs, summary statistics (geometric mean, minimum, median, maximum) for the titers are presented by assessment (Day 1, Day 22, or Day 43) and vaccine group for the overall study population and by age subgroup (6 months to <36 months; 3 years to <9 years).

The analysis model for GMTs was a general linear model on log10-transformed Day 22 or Day 43 titers as the outcome variable, with vaccine formulation, log-transformed pre-vaccination titer, and age subgroup as covariates. From this model, adjusted differences in the least square means (on the log scale) were produced with 95% confidence limits for each vaccine formulation versus the Arm F formulation (licensed dosage for adults). The estimated difference and the confidence limits were back-transformed to obtain an adjusted GMT ratio with 95% confidence limits.

Geometric Mean Ratio For the evaluation of GMRs, summary statistics (geometric mean, coefficient of variation, minimum, median, maximum) of the relative increase in titers are presented by assessment (Day 22 and Day 43) and vaccine group for the overall study population and by age subgroup (6 months to <36 months; 3 years to <9 years).

The analysis model for GMRs was the same as that used for the analysis of GMTs, with log10-transformed Day 22 titers/Day 1 titers and Day 43 titers/Day 1 titers as the outcome variable and excluding the pre-vaccination titer as the covariate.

Binary Endpoints The number and proportion of subjects achieving the binary endpoints (seroconversion or titer ≥1:40) were summarized by assessment (Day 22 and Day 43) and vaccine group for the overall study population and by age subgroup (6 months to <36 months; 3 years to <9 years). The associated 2-sided 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. No formal statistical hypothesis was tested.

Secondary Immunogenicity Endpoint Methodology All secondary immunogenicity endpoints (based on the Day 202 time point) were analyzed in the same manner as the primary immunogenicity endpoints.

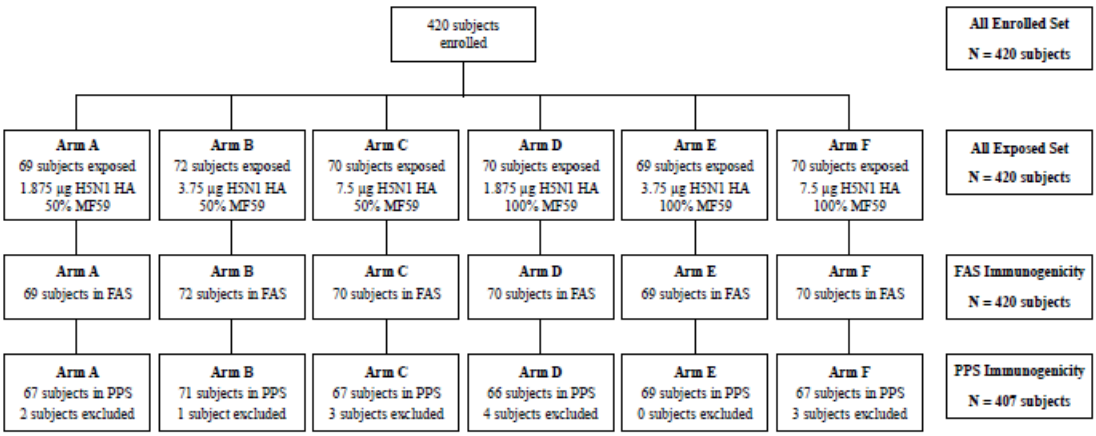
The statistical analysis was descriptive therefore, no inferential tests were in place. The immunogenicity analyses were performed in the PPS Immunogenicity, which was the primary population of interest for the primary and secondary immunogenicity analyses.

Results

Participant flow

A total of 420 subjects 6 months to <9 years of age were enrolled in the study (All Enrolled Set) and randomized in a 1:1:1:1:1:1 ratio to one of the 6 vaccine groups, stratified by age (6 months to <36 months and 3 years to <9 years) (Arms A to F). All of the 420 enrolled subjects received at least one study vaccination and were therefore included in the All Exposed Set. The majority of subjects (419/420 subjects, 99.8%) completed the study; all subjects received 2 doses of study vaccine.

Figure 1: Study Disposition Flowchart



Source: Table 14.1.1.1 and Table 14.1.1.1.1.
Abbreviations: FAS = Full Analysis Set; HA = hemagglutinin; PPS = Per Protocol Set.

Table 4: Study Disposition – As Randomized – All Enrolled Set

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) n (%)	Arm B (3.75 µg/50%) n (%)	Arm C (7.5 µg/50%) n (%)	Arm D (1.875 µg/100%) n (%)	Arm E (3.75 µg/100%) n (%)	Arm F (7.5 µg/100%) n (%)	Total n (%)
6 Months to <9 Years	**N=69**	**N=72**	**N=70**	**N=70**	**N=69**	**N=70**	**N=420**
Total number of subjects enrolled	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
Total number of subjects exposed	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
Completed the study	69 (100.0)	71 (98.6)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	419 (99.8)
Discontinuation from the study	**0**	**1 (1.4)**	**0**	**0**	**0**	**0**	**1 (0.2)**
Primary reason for discontinuation							
Death	0	1 (1.4)	0	0	0	0	1 (0.2)
6 Months to <36 Months	**N=35**	**N=35**	**N=35**	**N=35**	**N=36**	**N=34**	**N=210**
Total number of subjects enrolled	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
Total number of subjects exposed	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
Completed the study	35 (100.0)	34 (97.1)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	209 (99.5)
Discontinuation from the study	**0**	**1 (2.9)**	**0**	**0**	**0**	**0**	**1 (0.5)**
Primary reason for discontinuation							
Death	0	1 (2.9)	0	0	0	0	1 (0.5)
3 Years to <9 Years	**N=34**	**N=37**	**N=35**	**N=35**	**N=33**	**N=36**	**N=210**
Total number of subjects enrolled	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
Total number of subjects exposed	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
Completed the study	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)

Source: Table 14.1.1.2.
Abbreviations: ID = identification; N = total number of subjects; n = number of subjects with values in category.
Note 1: Enrolled subjects are all screened subjects who provided informed consent/assent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a subject ID.

There were 210 subjects in each of the two age cohorts in the All Enrolled Set. The vast majority of subjects (419/420 subjects, 99.8%) completed the study; 1 subject (0.2%) died during the study (not related to the study vaccine). All subjects received 2 doses of study vaccine.

Recruitment

Date of Study Initiation: 19 December 2020

Date of Study Completion: 15 April 2022

Participants were recruited in Estonia (2 centers) and in the Philippines (5 centers).

Conduct of the study

Major protocol deviations in the All-Enrolled Set are summarized in Table 5.

In the overall study population, 13 of 420 subjects (3.1%) reported at least 1 major protocol deviation; 8 of 210 subjects (3.8%) in the 6 months to <36 months age cohort and 5 of 210 subjects (2.4%) in the 3 years to <9 years age cohort reported at least 1 major protocol deviation.

Major protocol deviations were categorized as related or not related to COVID-19.

Major protocol deviations not related to COVID-19 were reported by 11 of 420 subjects (2.6%) in the overall study population (Table 5). The most commonly reported protocol deviation was in the "Procedures/Tests" category; 10 subjects (2.4%) had a serum sample collected outside of the time window specified in the protocol.

Major protocol deviations related to COVID-19 were reported by 3 of 420 subjects (0.7%) in the overall study population (Table 5).

All 13 subjects with major protocol deviations were excluded from the PPS.

Table 5: Major Protocol Deviation – As Randomized – All Enrolled Set

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) n (%)	Arm B (3.75 µg/50%) n (%)	Arm C (7.5 µg/50%) n (%)	Arm D (1.875 µg/100%) n (%)	Arm E (3.75 µg/100%) n (%)	Arm F (7.5 µg/100%) n (%)	Total n (%)
6 Months to <9 Years	N=69	N=72	N=70	N=70	N=69	N=70	N=420
Any major protocol deviation	2 (2.9)	1 (1.4)	3 (4.3)	4 (5.7)	0	3 (4.3)	13 (3.1)
Major protocol deviation (not related to COVID-19)	2 (2.9)	1 (1.4)	3 (4.3)	3 (4.3)	0	2 (2.9)	11 (2.6)
Disallowed medications	0	0	1 (1.4)	0	0	0	1 (0.2)
Procedures/tests	2 (2.9)	1 (1.4)	2 (2.9)	3 (4.3)	0	2 (2.9)	10 (2.4)
Visit schedule	2 (2.9)	1 (1.4)	2 (2.9)	2 (2.9)	0	1 (1.4)	8 (1.9)
Major COVID-19-related protocol deviation	0	0	0	2 (2.9)	0	1 (1.4)	3 (0.7)
Disallowed medications	0	0	0	0	0	0	0
Procedures/tests	0	0	0	2 (2.9)	0	1 (1.4)	3 (0.7)
Visit schedule	0	0	0	1 (1.4)	0	1 (1.4)	2 (0.5)
6 Months to <36 Months	N=35	N=35	N=35	N=35	N=36	N=34	N=210
Any major protocol deviation	1 (2.9)	1 (2.9)	1 (2.9)	2 (5.7)	0	3 (8.8)	8 (3.8)
Major protocol deviation (not related to COVID-19)	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	0	2 (5.9)	6 (2.9)
Disallowed medications	0	0	0	0	0	0	0
Procedures/tests	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.9)	0	2 (5.9)	6 (2.9)
Visit schedule	1 (2.9)	1 (2.9)	1 (2.9)	0	0	1 (2.9)	4 (1.9)
Major COVID-19-related protocol deviation	0	0	0	1 (2.9)	0	1 (2.9)	2 (1.0)
Disallowed medications	0	0	0	0	0	0	0
Procedures/tests	0	0	0	1 (2.9)	0	1 (2.9)	2 (1.0)
Visit schedule	0	0	0	1 (2.9)	0	1 (2.9)	2 (1.0)
3 Years to <9 Years	N=34	N=37	N=35	N=35	N=33	N=36	N=210
Any major protocol deviation	1 (2.9)	0	2 (5.7)	2 (5.7)	0	0	5 (2.4)
Major protocol deviation (not related to COVID-19)	1 (2.9)	0	2 (5.7)	2 (5.7)	0	0	5 (2.4)
Disallowed medications	0	0	1 (2.9)	0	0	0	1 (0.5)
Procedures/tests	1 (2.9)	0	1 (2.9)	2 (5.7)	0	0	4 (1.9)
Visit schedule	1 (2.9)	0	1 (2.9)	2 (5.7)	0	0	4 (1.9)
Major COVID-19-related protocol deviation	0	0	0	1 (2.9)	0	0	1 (0.5)
Disallowed medications	0	0	0	0	0	0	0
Procedures/tests	0	0	0	1 (2.9)	0	0	1 (0.5)
Visit schedule	0	0	0	0	0	0	0

Source: Table 14.1.1.8.

Abbreviations: ID = identification; N = total number of subjects; n = number of subjects with values in category.

Note 1: The All Enrolled Set is all screened subjects who provided informed consent/assent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a subject ID.

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

A low percentage (3.1%) of subjects reported major deviations; these were classified as COVID-19-related (0.7%) and not COVID-related (2.6%), and mostly commonly belonged to the "Procedures/Tests" category being outside the planned window. Therefore, no potential impact on quality of study data is foreseen.

Baseline data

The demographic and baseline characteristics of the All Enrolled Set are summarized for the overall study population in Table 6

This study was conducted at 2 centers in Estonia and 5 centers in the Philippines: 100 of 420 subjects (23.8%) were enrolled in Estonia and 320 of 420 subjects (76.2%) were enrolled in the Philippines (Table 6).

The mean age of the study population was 49.3 months (SD: 30.82 months) and the range was 7 months to 8 years 11 months, which was consistent with the intended study population (6 months to <9 years of age). The stratification strategy was designed to ensure the age cohorts were of equal size. The resulting age distribution met this intention, with 50% of subjects being in the 6 months to <36 months age cohort (N=210) and 50% of subjects being in the 3 years to <9 years age cohort (N=210). As planned, there were approximately 70 subjects randomized to each of the 6 vaccine groups, with approximately 35 subjects per age cohort within a vaccine group.

Demographic and baseline characteristics are similar and balanced across vaccines subgroups, with the study enrolling more male subjects (228/420 subjects, 54.3%) than female subjects (192/420 subjects, 45.7%).

The majority of the study population was Asian (319/420 subjects, 76.0%), followed by White (100/420 subjects, 23.8%). All subjects were of "Not Hispanic or Latino" ethnicity.

The majority of subjects (408/420 subjects, 97.1%) had not received an influenza vaccination in the past 2 years.

There were no major differences in the distribution of demographic and baseline characteristics across the 6 vaccine groups in the overall study population. The proportion of male subjects was higher than female subjects in Arms A to E, but lower in Arm F (Table 6). A similar distribution of demographic and baseline characteristics across the 6 vaccine groups was observed within the 6 months to <36 months and 3 years to <9 years age cohorts (Table 7).

Table 6: Demographics and Baseline Characteristics in Subjects 6 Months to <9 Years of Age – As Randomized – All Enrolled Set

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) N=69 n (%)	Arm B (3.75 µg/50%) N=72 n (%)	Arm C (7.5 µg/50%) N=70 n (%)	Arm D (1.875 µg/100%) N=70 n (%)	Arm E (3.75 µg/100%) N=69 n (%)	Arm F (7.5 µg/100%) N=70 n (%)	Total N=420 n (%)
Age (months)							
Mean (SD)	48.2 (28.80)	50.9 (31.61)	47.1 (30.90)	48.8 (31.81)	49.9 (30.79)	50.6 (31.77)	49.3 (30.82)
Min, max	11, 106	9, 106	7, 103	8, 104	9, 107	9, 106	7, 107
Age category (n [%])							
6 months to <36 months	35 (50.7)	35 (48.6)	35 (50.0)	35 (50.0)	36 (52.2)	34 (48.6)	210 (50.0)
3 years to <9 years	34 (49.3)	37 (51.4)	35 (50.0)	35 (50.0)	33 (47.8)	36 (51.4)	210 (50.0)
Gender (n [%])							
Male	38 (55.1)	46 (63.9)	37 (52.9)	39 (55.7)	38 (55.1)	30 (42.9)	228 (54.3)
Female	31 (44.9)	26 (36.1)	33 (47.1)	31 (44.3)	31 (44.9)	40 (57.1)	192 (45.7)
Race (n [%])							
American Indian or Alaska Native	0	0	0	0	0	0	0
Asian	52 (75.4)	56 (77.8)	53 (75.7)	53 (75.7)	52 (75.4)	53 (75.7)	319 (76.0)
Black or African American	0	0	0	0	0	1 (1.4)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
White	17 (24.6)	16 (22.2)	17 (24.3)	17 (24.3)	17 (24.6)	16 (22.9)	100 (23.8)
Other	0	0	0	0	0	0	0
Ethnicity (n [%])							
Hispanic or Latino	0	0	0	0	0	0	0
Not Hispanic or Latino	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
Not reported	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0
(H5N1 HA antigen dose/MF59 content)	**Arm A (1.875 µg/50%) N=69 n (%)**	**Arm B (3.75 µg/50%) N=72 n (%)**	**Arm C (7.5 µg/50%) N=70 n (%)**	**Arm D (1.875 µg/100%) N=70 n (%)**	**Arm E (3.75 µg/100%) N=69 n (%)**	**Arm F (7.5 µg/100%) N=70 n (%)**	**Total N=420 n (%)**
Received an influenza vaccination in the past 2 years (n [%])							
Yes	1 (1.4)	0	3 (4.3)	3 (4.3)	3 (4.3)	2 (2.9)	12 (2.9)
No	68 (98.6)	72 (100.0)	67 (95.7)	67 (95.7)	66 (95.7)	68 (97.1)	408 (97.1)
Body mass index (kg/m²)							
Mean (SD)	16.31 (2.669)	16.29 (2.698)	16.50 (2.865)	15.69 (1.959)	15.61 (1.940)	16.07 (2.644)	16.08 (2.498)
Median	16.12	15.94	15.82	15.38	15.62	15.69	15.72
Country (n [%])							
Estonia	17 (24.6)	16 (22.2)	17 (24.3)	17 (24.3)	17 (24.6)	16 (22.9)	100 (23.8)
Philippines	52 (75.4)	56 (77.8)	53 (75.7)	53 (75.7)	52 (75.4)	54 (77.1)	320 (76.2)

Source: Table 14.1.1.3.

Abbreviations: ID = identification; max = maximum; min = minimum; N = total number of subjects; n = number of subjects with values in category; PPS = Per Protocol Set; SD = standard deviation.

Note 1: The All Enrolled Set is all screened subjects who provided informed consent/assent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a subject ID.

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

Table 7: Demographics and Baseline Characteristics in Subjects 6 Months to<36 Months of Age and 3 Years to <9 Years of Age – As Randomized – All Enrolled Set

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) n (%)	Arm B (3.75 µg/50%) n (%)	Arm C (7.5 µg/50%) n (%)	Arm D (1.875 µg/100%) n (%)	Arm E (3.75 µg/100%) n (%)	Arm F (7.5 µg/100%) n (%)	Total n (%)
6 Months to <36 Months	**N=35**	**N=35**	**N=35**	**N=35**	**N=36**	**N=34**	**N=210**
Age (months)							
Mean (SD)	22.9 (6.80)	22.5 (7.93)	20.3 (8.85)	21.8 (7.60)	23.9 (7.37)	22.1 (7.30)	22.2 (7.66)
Min, max	11, 32	9, 34	7, 34	8, 35	9, 35	9, 35	7, 35
Gender (n [%])							
Male	20 (57.1%)	22 (62.9%)	22 (62.9%)	21 (60.0%)	19 (52.8%)	17 (50.0%)	121 (57.6%)
Female	15 (42.9%)	13 (37.1%)	13 (37.1%)	14 (40.0%)	17 (47.2%)	17 (50.0%)	89 (42.4%)
Race (n [%])							
American Indian or Alaska Native	0	0	0	0	0	0	0
Asian	27 (77.1)	27 (77.1)	26 (74.3)	26 (74.3)	27 (75.0)	27 (79.4)	160 (76.2)
Black or African American	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
White	8 (22.9)	8 (22.9)	9 (25.7)	9 (25.7)	9 (25.0)	7 (20.6)	50 (23.8)
Other	0	0	0	0	0	0	0
Ethnicity (n [%])							
Hispanic or Latino	0	0	0	0	0	0	0
Not Hispanic or Latino	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
Not reported	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) n (%)	Arm B (3.75 µg/50%) n (%)	Arm C (7.5 µg/50%) n (%)	Arm D (1.875 µg/100%) n (%)	Arm E (3.75 µg/100%) n (%)	Arm F (7.5 µg/100%) n (%)	Total n (%)
Received an influenza vaccination in the past 2 years (n [%])							
Yes	1 (2.9%)	0	2 (5.7%)	1 (2.9%)	2 (5.6%)	1 (2.9%)	7 (3.3%)
No	34 (97.1%)	35 (100.0%)	33 (94.3%)	34 (97.1%)	34 (94.4%)	33 (97.1%)	203 (96.7%)
Body mass index (kg/m^2)							
Mean (SD)	16.60 (2.489)	16.25 (1.985)	16.39 (2.172)	15.90 (1.877)	15.89 (1.870)	16.12 (1.881)	16.19 (2.049)
Median	16.69	16.02	16.22	15.69	15.77	16.27	16.02
Country (n [%])							
Estonia	8 (22.9%)	8 (22.9%)	9 (25.7%)	9 (25.7%)	9 (25.0%)	7 (20.6%)	50 (23.8%)
Philippines	27 (77.1%)	27 (77.1%)	26 (74.3%)	26 (74.3%)	27 (75.0%)	27 (79.4%)	160 (76.2%)
3 Years to <9 Years	**N=34**	**N=37**	**N=35**	**N=35**	**N=33**	**N=36**	**N=210**
Age (months)							
Mean (SD)	74.2 (16.78)	77.8 (19.52)	73.9 (19.48)	75.9 (22.07)	78.4 (18.85)	77.4 (20.24)	76.3 (19.42)
Min, max	44, 106	39, 106	40, 103	36, 104	39, 107	36, 106	36, 107
Gender (n [%])							
Male	18 (52.9)	24 (64.9)	15 (42.9)	18 (51.4)	19 (57.6)	13 (36.1)	107 (51.0)
Female	16 (47.1)	13 (35.1)	20 (57.1)	17 (48.6)	14 (42.4)	23 (63.9)	103 (49.0)
Race (n [%])							
American Indian or Alaska Native	0	0	0	0	0	0	0
Asian	25 (73.5)	29 (78.4)	27 (77.1)	27 (77.1)	25 (75.8)	26 (72.2)	159 (75.7)
Black or African American	0	0	0	0	0	1 (2.8)	1 (0.5)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0
White	9 (26.5)	8 (21.6)	8 (22.9)	8 (22.9)	8 (24.2)	9 (25.0)	50 (23.8)
Other	0	0	0	0	0	0	0

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) n (%)	Arm B (3.75 µg/50%) n (%)	Arm C (7.5 µg/50%) n (%)	Arm D (1.875 µg/100%) n (%)	Arm E (3.75 µg/100%) n (%)	Arm F (7.5 µg/100%) n (%)	Total n (%)
Ethnicity (n [%])							
Hispanic or Latino	0	0	0	0	0	0	0
Not Hispanic or Latino	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
Not reported	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0
Received an influenza vaccination in the past 2 years (n [%])							
Yes	0	0	1 (2.9)	2 (5.7)	1 (3.0)	1 (2.8)	5 (2.4)
No	34 (100.0)	37 (100.0)	34 (97.1)	33 (94.3)	32 (97.0)	35 (97.2)	205 (97.6)
Body mass index (kg/m^2)							
Mean (SD)	16.01 (2.849)	16.33 (3.260)	16.60 (3.452)	15.48 (2.044)	15.31 (1.998)	16.02 (3.232)	15.97 (2.879)
Median	16.02	15.41	15.70	15.15	15.43	15.03	15.44
Country (n [%])							
Estonia	9 (26.5)	8 (21.6)	8 (22.9)	8 (22.9)	8 (24.2)	9 (25.0)	50 (23.8)
Philippines	25 (73.5)	29 (78.4)	27 (77.1)	27 (77.1)	25 (75.8)	27 (75.0)	160 (76.2)

Source: Table 14.1.1.3.

Abbreviations: ID = identification; max = maximum; min = minimum; N = total number of subjects; n = number of subjects with values in category; PPS = Per Protocol Set; SD = standard deviation.

Note 1: The All Enrolled Set is all screened subjects who provided informed consent/assent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a subject ID.

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

Approximately 70 subjects randomized to each of the 6 vaccine groups, with approximately 35 subjects per age cohort within a vaccine group. The majority of subjects were enrolled in the Philippines (76.2%) and the others in Estonia (23.8%). Therefore, the more represented ethnicity was Asian followed by White. None of the participants were "Hispanic or Latino" ethnicity.

Subjects with abnormal function of the immune system due to any cause were excluded; though acceptable, this limits generalizability of study results to immunocompromised paediatric population.

The great majority of subjects (97.1%) had not received an influenza vaccination in the previous 2 years; no information is provided regarding proportion of subjects ever been vaccinated during lifetime.

Other Baseline Characteristics

Medical History and Concurrent Illnesses

At least 1 medical disorder was reported as medical history for 104 of 420 subjects (24.8%) in the All Enrolled Set. The proportion of subjects with medical disorders was generally similar between the 6 vaccine groups (Arm A: 21.7%; Arm B: 23.6%; Arm C: 31.4%; Arm D: 25.7%; Arm E: 23.2%; Arm F: 22.9%). The types of medical disorders reported as medical history were reflective of the population age.

Prior Medications

Use of at least 1 prior medication was reported by 154 of 420 subjects (36.7%) in the Overall Safety Set. The use of prior medications was generally similar between the 6 vaccine groups (Arm A: 39.1%; Arm B: 37.5%; Arm C: 28.6%; Arm D: 42.9%; Arm E: 33.3%; Arm F: 38.6%). The most commonly reported types of prior medication were viral vaccines (112/420 subjects, 26.7%) and ascorbic acid (including combinations; 25/420 subjects, 6.0%).

Concomitant Medications

During the treatment period (Day 1 through Day 43), use of at least 1 concomitant medication was reported by 123 of 420 subjects (29.3%) in the Overall Safety Set. The use of concomitant medications was similar between the 6 vaccine groups (Arm A: 31.9%; Arm B: 31.9%; Arm C: 28.6%; Arm D: 30.0%; Arm E: 26.1%; Arm F: 27.1%). The most commonly reported concomitant medications were paracetamol (52/420 subjects, 12.4%) and ascorbic acid (24/420 subjects, 5.7%).

During the entire study period (Day 1 through Day 387), use of at least 1 concomitant medication was reported by 154 of 420 subjects (36.7%) in the Overall Safety Set. The use of concomitant medications was similar between the 6 vaccine groups (Arm A: 37.7%; Arm B: 37.5%; Arm C: 37.1%; Arm D: 37.1%; Arm E: 33.3%; Arm F: 37.1%). The most commonly reported concomitant medications were viral vaccines (26.7%), paracetamol (57/420 subjects, 13.6%) and ascorbic acid (24/420 subjects, 5.7%).

Measurements of Treatment Compliance

All study vaccines were administered by study personnel who were qualified to perform the procedure under applicable local laws and regulations for the study site.

Compliance was very high, with all of the 420 enrolled subjects receiving both the first and second study vaccination.

Outcomes and estimation

Table 8: Overview of Immunogenicity Sets Analyzed – As Randomized – All Enrolled Set

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) n (%)	Arm B (3.75 µg/50%) n (%)	Arm C (7.5 µg/50%) n (%)	Arm D (1.875 µg/100%) n (%)	Arm E (3.75 µg/100%) n (%)	Arm F (7.5 µg/100%) n (%)	Total n (%)
6 Months to <9 Years	**N=69**	**N=72**	**N=70**	**N=70**	**N=69**	**N=70**	**N=420**
All Enrolled Set	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
All Exposed Set	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
FAS Immunogenicity	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
PPS Immunogenicity	67 (97.1)	71 (98.6)	67 (95.7)	66 (94.3)	69 (100.0)	67 (95.7)	407 (96.9)
6 Months to <36 Months	**N=35**	**N=35**	**N=35**	**N=35**	**N=36**	**N=34**	**N=210**
All Enrolled Set	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
All Exposed Set	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
FAS Immunogenicity	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
PPS Immunogenicity	34 (97.1)	34 (97.1)	34 (97.1)	33 (94.3)	36 (100.0)	31 (91.2)	202 (96.2)
3 Years to <9 Years	**N=34**	**N=37**	**N=35**	**N=35**	**N=33**	**N=36**	**N=210**
All Enrolled Set	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
All Exposed Set	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
FAS Immunogenicity	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
PPS Immunogenicity	33 (97.1)	37 (100.0)	33 (94.3)	33 (94.3)	33 (100.0)	36 (100.0)	205 (97.6)

Source: Table 14.1.1.1 and Table 14.1.1.1.1.

Abbreviations: FAS = Full Analysis Set; ID = identification; N = total number of subjects; n = number of subjects with values in category; PPS = Per Protocol Set.

Note 1: The All Enrolled Set is all screened subjects who provided informed consent/assent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a subject ID.

Note 2: The All Exposed Set is all subjects in the All Enrolled Set who received at least one dose of study vaccination.

Note 3: The FAS Immunogenicity is all subjects in the All Enrolled Set who were randomized, received at least one study vaccination, and provided immunogenicity data at any time point.

Note 4: The PPS Immunogenicity is all subjects in the FAS Immunogenicity who: correctly received the vaccine (ie, received the vaccine to which the subject was randomized and at the scheduled time points); provided at least the baseline and one postbaseline blood sample, with evaluable immunogenicity data; had no protocol deviations leading to exclusion as defined prior to unblinding/analysis; and were not excluded due to other reasons defined prior to unblinding or analysis.

Baseline Immune Status

Baseline immune responses before vaccination on Day 1, as measured by HI and MN assay, against the homologous H5N1 strain are reported below (Table 9).

Table 9: Baseline Immune Response in Paediatric Subjects Against the Homologous H5N1 strain by HI and MN Assay (As Treated – PPS Immunogenicity)

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%)	Arm B (3.75 µg/50%)	Arm C (7.5 µg/50%)	Arm D (1.875 µg/100%)	Arm E (3.75 µg/100%)	Arm F (7.5 µg/100%)
6 Months to <36 Months	**N=34**	**N=34**	**N=34**	**N=33**	**N=36**	**N=31**
HI GMT Day 1 (95% CI)	5.10 (4.9, 5.3)	5.00 (4.8, 5.2)	5.42 (5.2, 5.7)	5.11 (4.9, 5.3)	5.00 (4.8, 5.2)	5.00 (4.8, 5.2)
Percentage of subjects with HI titre ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)	0.0 (0.00, 11.22)
MN GMT Day 1 (95% CI)	5.00 (4.7, 5.3)	5.00 (4.7, 5.3)	5.26 (4.9, 5.6)	5.21 (4.9, 5.6)	5.10 (4.8, 5.4)	5.29 (4.9, 5.7)
Percentage of subjects with MN titre ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)	0.0 (0.00, 11.22)
3 Years to <9 Years	**N=33**	**N=37**	**N=33**	**N=33**	**N=33**	**N=36**
HI GMT Day 1 (95% CI)	5.00 (4.6, 5.4)	5.00 (4.7, 5.4)	5.00 (4.6, 5.4)	5.00 (4.6, 5.4)	5.00 (4.6, 5.4)	5.45 (5.1, 5.9)
Percentage of subjects with HI titre ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.58)	0.0 (0.00, 9.49)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	2.8 (0.07, 14.53)
MN GMT Day 1 (95% CI)	5.38 (4.9, 5.9)	5.54 (5.1, 6.0)	5.49 (5.0, 6.0)	5.11 (4.7, 5.6)	5.16 (4.7, 5.7)	5.35 (4.9, 5.8)
Percentage of subjects with MN titre ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.58)	0.0 (0.00, 9.49)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)

Source: Section 5.3.5.1 CSR V87_30

Abbreviations: CI = confidence interval; GMT = geometric mean titre; HI = hemagglutination inhibition; MN = microneutralization; N = total number of subjects; PPS = Per Protocol Set.

Note 1: The PPS Immunogenicity is all subjects in the FAS Immunogenicity who: correctly received the vaccine (ie, received the vaccine to which the subject was randomized and at the scheduled time points); provided at least the baseline and one postbaseline blood sample, with evaluable immunogenicity data; have no protocol deviations leading to exclusion as defined prior to unblinding/analysis; and are not excluded due to other reasons defined prior to unblinding or analysis.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Immune responses before vaccination on Day 1, measured by HI and MN assay, against the homologous H5/N1 strain are very low and similar across study arms, with no difference noted with regard to age. This suggests that study participants were a naive population.

Comparison of Immunogenicity Results of All Studies

Immunogenicity Results (Study V87_30) Immunological responses to the different doses of antigen and adjuvant contained in the 6 vaccine formulations of aH5N1 were evaluated using HI and MN assays with egg-derived H5N1 target virus. Blood samples were obtained on Day 1 (prior to the first vaccination), on Day 22 (3 weeks after the first vaccination, prior to the second vaccination), and on Day 43 (3 weeks after the second vaccination). HI and MN antibody titers on Days 22 and 43 were compared with the baseline antibody titers to evaluate immunogenicity.

The immunogenicity objectives were evaluated using the PPS subset of subjects.

Primary Immunogenicity Endpoints

The primary immunogenicity objective was to assess by total population and by age cohort, the antibody responses to each of the study vaccines prior to (Day 1) and at 3 weeks after the first or second vaccination (Day 22 or Day 43), as measured by HI and MN assays.

GMTs and GMRs for HI Titers (Day 1 to Day 43)

The GMTs measured by HI assay against the H5N1 pandemic influenza homologous strain at Day 1, Day 22, and Day 43, along with the Day 22/Day 1 and Day 43/Day 1 GMRs, are shown for the overall study population and by age cohort in the Table 10.

The HI GMT and GMR results of these analyses are adjusted estimates.

Subjects 6 Months to <9 Years of Age

The **Day 1** HI titers against the homologous H5/N1 pandemic influenza strain were very low, bordering on the LLOQ of 10, in the 6 vaccine groups in the overall study population.

At **Day 22**, increases in HI GMTs from Day 1 in the 6 vaccine groups were minimal, with the Day 22/Day 1 GMRs ranging from 1.11 to 1.29.

At Day 43:

• Increases in HI GMTs from Day 1 were observed in all 6 vaccine groups.

• The Day 43/Day 1 GMRs ranged from 13.77 to 24.98.

• The Day 43/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 23.14 to 24.98) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 13.77 to 16.38), suggesting that MF59 content is associated with the magnitude of the immune response.

Subjects 6 Months to <36 Months of Age

In the 6 months to <36 months age cohort, the HI titers against the homologous H5N1 pandemic influenza strain were very low, bordering on the LLOQ of 10, in the 6 vaccine groups at **Day 1**.

Increases in HI GMTs at **Day 22** were minimal, with the Day 22/Day 1 GMRs ranging from 1.05 to 1.30 (Table 10).

At **Day 43:**

• Increases in HI GMTs from Day 1 were observed in all 6 vaccine groups, with the Day 43/Day 1 GMRs ranging from 18.27 to 31.39.

• The Day 43/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 23.94 to 31.39) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 18.27 to 19.62).

Subjects 3 Years to <9 Years of Age

The HI titers against the homologous H5/N1 pandemic influenza strain were very low, bordering on the LLOQ of 10, in the 6 vaccine groups at **Day 1**. Increases in HI GMTs at **Day 22** were minimal, with the Day 22/Day 1 GMRs ranging from 1.08 to 1.29 (Table 10).

At Day 43:

• Increases in HI GMTs from Day 1 were observed in all 6 vaccine groups, with the Day 43/Day 1 GMRs ranging from 9.83 to 23.34.

• The Day 43/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 19.75 to 23.34) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 9.83 to 14.27).

• Across all vaccine groups, increases in HI GMTs tended to be higher in the 6 months to <36 months age cohort (Day 43/Day 1 GMRs, range: 18.27 to 31.39) than in the 3 years to <9 years age cohort (Day 43/Day 1 GMRs, range: 9.83 to 23.34).

Table 10: Pre- and Postvaccination GMTs and GMRs, Overall and by Age Cohort (HI Assay Against the Homologous H5N1 Strain) – As Treated – PPS Immunogenicity

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%)	Arm B (3.75 µg/50%)	Arm C (7.5 µg/50%)	Arm D (1.875 µg/100%)	Arm E (3.75 µg/100%)	Arm F (7.5 µg/100%)
6 Months to <9 Years	**N=67**	**N=71**	**N=67**	**N=66**	**N=69**	**N=67**
HI GMT Day 1 (95% CI)	5.05 (4.8, 5.3)	5.00 (4.8, 5.2)	5.21 (5.0, 5.4)	5.05 (4.8, 5.3)	5.00 (4.8, 5.2)	5.24 (5.0, 5.5)
HI GMT Day 22 (95% CI)	5.61 (4.9, 6.4)	6.21 (5.5, 7.0)	5.98 (5.3, 6.8)	6.17 (5.4, 7.0)	6.47 (5.7, 7.3)	5.78 (5.1, 6.6)
HI GMR Day 22/Day 1 (95% CI)	1.11 (1.0, 1.3)	1.24 (1.1, 1.4)	1.15 (1.0, 1.3)	1.22 (1.1, 1.4)	1.29 (1.1, 1.5)	1.11 (1.0, 1.3)
HI GMT Day 43 (95% CI)	81.10 (58.3, 112.8)	68.06 (49.4, 93.8)	86.70 (62.3, 120.7)	122.43 (87.8, 170.7)	123.37 (89.1, 170.8)	123.61 (88.8, 172.1)
HI GMR Day 43/Day 1 (95% CI)	16.14 (11.5, 22.6)	13.77 (9.9, 19.1)	16.38 (11.7, 23.0)	24.35 (17.3, 34.2)	24.98 (17.9, 34.8)	23.14 (16.5, 32.4)
6 Months to <36 Months	**N=34**	**N=34**	**N=34**	**N=33**	**N=36**	**N=31**
HI GMT Day 1 (95% CI)	5.10 (4.9, 5.3)	5.00 (4.8, 5.2)	5.42 (5.2, 5.7)	5.11 (4.9, 5.3)	5.00 (4.8, 5.2)	5.00 (4.8, 5.2)
HI GMT Day 22 (95% CI)	5.59 (4.7, 6.6)	6.14 (5.2, 7.3)	5.51 (4.6, 6.6)	6.23 (5.2, 7.4)	6.55 (5.5, 7.8)	5.78 (4.8, 6.9)
HI GMR Day 22/Day 1 (95% CI)	1.10 (0.9, 1.3)	1.21 (1.0, 1.4)	1.05 (0.9, 1.3)	1.22 (1.0, 1.5)	1.30 (1.1, 1.5)	1.14 (1.0, 1.4)
HI GMT Day 43 (95% CI)	93.22 (56.5, 153.7)	98.37 (59.6, 162.4)	102.28 (61.5, 170.1)	129.72 (78.1, 215.5)	157.44 (96.7, 256.3)	120.07 (71.0, 202.9)
HI GMR Day 43/Day 1 (95% CI)	18.27 (11.1, 30.1)	19.62 (11.9, 32.4)	19.02 (11.5, 31.4)	25.41 (15.3, 42.2)	31.39 (19.3, 51.1)	23.94 (14.2, 40.4)
3 Years to <9 Years	**N=33**	**N=37**	**N=33**	**N=33**	**N=33**	**N=36**
HI GMT Day 1 (95% CI)	5.00 (4.6, 5.4)	5.00 (4.7, 5.4)	5.00 (4.6, 5.4)	5.00 (4.6, 5.4)	5.00 (4.6, 5.4)	5.45 (5.1, 5.9)
HI GMT Day 22 (95% CI)	5.61 (4.6, 6.8)	6.32 (5.3, 7.6)	6.29 (5.2, 7.6)	6.10 (5.0, 7.4)	6.42 (5.3, 7.8)	5.91 (4.9, 7.1)
HI GMR Day 22/Day 1 (95% CI)	1.12 (0.9, 1.4)	1.26 (1.0, 1.5)	1.26 (1.0, 1.5)	1.22 (1.0, 1.5)	1.29 (1.0, 1.6)	1.08 (0.9, 1.3)
HI GMT Day 43 (95% CI)	70.21 (45.5, 108.4)	48.35 (32.1, 72.9)	69.40 (44.9, 107.2)	114.85 (74.4, 177.4)	97.17 (62.9, 150.1)	129.15 (84.9, 196.6)
HI GMR Day 43/Day 1 (95% CI)	14.27 (9.0, 22.6)	9.83 (6.4, 15.2)	14.10 (8.9, 22.3)	23.34 (14.7, 37.0)	19.75 (12.5, 31.3)	21.98 (14.2, 34.1)

Source: Table 14.2.1.1.

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; FAS = Full Analysis Set; HI = hemagglutination inhibition; N = total number of subjects; n = number of subjects with values in category; PPS = Per Protocol Set.

Note 1: The PPS Immunogenicity is all subjects in the FAS Immunogenicity who: correctly received the vaccine (ie, received the vaccine to which the subject was randomized and at the scheduled time points); provided at least the baseline and one postbaseline blood sample, with evaluable immunogenicity data; have no protocol deviations leading to exclusion as defined prior to unblinding/analysis; and are not excluded due to other reasons defined prior to unblinding or analysis.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Note 3: Adjusted GMTs and GMRs were calculated based on the log-transformed antibody titers at Day 22 and Day 43 using an ANCOVA model that included the log-transformed prevaccination antibody titer, age cohort, and vaccine group.

Percentage of Subjects With HI Seroconversion and Percentage of Subjects with HI Titer ≥1:40 (Day 1 to Day 43)

Percentage of Subjects With HI Seroconversion D1 to D43

Seroconversion was defined as non-detectable titer at D1 to ≥1:40, or 4-fold increase from a detectable Day 1 titer, as measured by HI assay.

Because of the very low HI GMTs at Day 1, there were no differences between the percentage of subjects with seroconversion and the percentage of subjects with HI titer ≥1:40 at Day 22 or Day 43 in the overall study population or either of the age cohorts.

Percentage of Subjects with HI Titer ≥1:40 (Day 1 to Day 43)

Subjects 6 Months to <9 Years of Age

At **Day 1**, the percentage of subjects with HI titer ≥1:40 was ≤1.5% across all vaccine groups in the overall study population (Table 11).

In line with the minimal increases in HI GMTs observed at Day 22 (Table 10), the percentage of subjects with HI titer ≥1:40 at **Day 22** was also low (≤4.5%) across all vaccine groups (Table 11).

At **Day 43:**

• The percentage of subjects with HI titer ≥1:40 increased from Day 1 across all 6 vaccine groups, ranging from 74.6% to 90.9%.

• The percentages of subjects with HI titer ≥1:40 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 86.6% to 90.9%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 74.6% to 82.1%).

Subjects 6 Months to <36 Months of Age

In the 6 months to <36 months age cohort, no subjects had an HI titer ≥1:40 at **Day 1** in any of the vaccine groups (Table 11). At **Day 22**, the percentage of subjects with HI titer ≥1:40 was low (≤3.2%) across the 6 vaccine groups.

At **Day 43:**

• The percentage of subjects with HI titer ≥1:40 increased from Day 1 in all 6 vaccine groups, ranging from 79.4% to 93.9%.

• The percentages of subjects with HI titer ≥1:40 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 86.1% to 93.9%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 79.4% to 82.4%).

Subjects 3 Years to <9 Years of Age

In the 3 years to <9 years age cohort, the percentage of subjects with HI titer ≥1:40 was ≤1.5% at **Day 1** across all 6 vaccine groups (Table 11). At **Day 22**, the percentage of subjects with HI titer ≥1:40 was low (≤6.1%) across the 6 vaccine groups.

At **Day 43:**

• The percentage of subjects with HI titer ≥1:40 increased from Day 1 in all 6 vaccine groups, ranging from 67.6% to 87.9%.

• The percentages of subjects with HI titer ≥1:40 consistently tended to higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 86.1% to 87.9%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 67.6% to 84.8%).

• The percentage of subjects with HI titer ≥1:40 tended to be higher in the vaccine groups in the 6 months to <36 months age cohort (79.4% to 93.9%) than in the 3 years to <9 years age cohort (67.6% to 87.9%).

Table 11: Percentage of Subjects With Seroconversion and Percentage of Subjects With HI Titer ≥1:40, Overall and by Age Cohort (HI Assay Against the Homologous H5N1 Strain) – As Treated – PPS Immunogenicity

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%)	Arm B (3.75 µg/50%)	Arm C (7.5 µg/50%)	Arm D (1.875 µg/100%)	Arm E (3.75 µg/100%)	Arm F (7.5 µg/100%)
6 Months to <9 Years	**N=67**	**N=71**	**N=67**	**N=66**	**N=69**	**N=67**
Percentage of subjects with seroconversion at Day 22 (95% CI)	0.0 (0.00, 5.36)	4.2 (0.88, 11.86)	3.0 (0.36, 10.37)	4.5 (0.95, 12.71)	1.4 (0.04, 7.81)	3.0 (0.36, 10.37)
Percentage of subjects with seroconversion at Day 43 (95% CI)	82.1 (70.80, 90.39)	74.6 (62.92, 84.23)	77.6 (65.78, 86.89)	90.9 (81.26, 96.59)	87.0 (76.68, 93.86)	86.6 (76.03, 93.67)
Percentage of subjects with HI titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 5.36)	0.0 (0.00, 5.06)	0.0 (0.00, 5.36)	0.0 (0.00, 5.44)	0.0 (0.00, 5.21)	1.5 (0.04, 8.04)
Percentage of subjects with HI titer ≥1:40 at Day 22 (95% CI)	0.0 (0.00, 5.36)	4.2 (0.88, 11.86)	3.0 (0.36, 10.37)	4.5 (0.95, 12.71)	1.4 (0.04, 7.81)	3.0 (0.36, 10.37)
Percentage of subjects with HI titer ≥1:40 at Day 43 (95% CI)	82.1 (70.80, 90.39)	74.6 (62.92, 84.23)	77.6 (65.78, 86.89)	90.9 (81.26, 96.59)	87.0 (76.68, 93.86)	86.6 (76.03, 93.67)
6 Months to <36 Months	**N=34**	**N=34**	**N=34**	**N=33**	**N=36**	**N=31**
Percentage of subjects with seroconversion at Day 22 (95% CI)	0.0 (0.00, 10.28)	2.9 (0.07, 15.33)	0.0 (0.00, 10.28)	3.0 (0.08, 15.76)	0.0 (0.00, 9.74)	3.2 (0.08, 16.70)
Percentage of subjects with seroconversion at Day 43 (95% CI)	79.4 (62.10, 91.30)	82.4 (65.47, 93.24)	79.4 (62.10, 91.30)	93.9 (79.77, 99.26)	86.1 (70.50, 95.33)	87.1 (70.17, 96.37)
Percentage of subjects with HI titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)	0.0 (0.00, 11.22)
Percentage of subjects with HI titer ≥1:40 at Day 22 (95% CI)	0.0 (0.00, 10.28)	2.9 (0.07, 15.33)	0.0 (0.00, 10.28)	3.0 (0.08, 15.76)	0.0 (0.00, 9.74)	3.2 (0.08, 16.70)
Percentage of subjects with HI titer ≥1:40 at Day 43 (95% CI)	79.4 (62.10, 91.30)	82.4 (65.47, 93.24)	79.4 (62.10, 91.30)	93.9 (79.77, 99.26)	86.1 (70.50, 95.33)	87.1 (70.17, 96.37)
3 Years to <9 Years	**N=33**	**N=37**	**N=33**	**N=33**	**N=33**	**N=36**
Percentage of subjects with seroconversion at Day 22 (95% CI)	0.0 (0.00, 10.58)	5.4 (0.66, 18.19)	6.1 (0.74, 20.23)	6.1 (0.74, 20.23)	3.0 (0.08, 15.76)	2.8 (0.07, 14.53)
Percentage of subjects with seroconversion at Day 43 (95% CI)	84.8 (68.10, 94.89)	67.6 (50.21, 81.99)	75.8 (57.74, 88.91)	87.9 (71.80, 96.60)	87.9 (71.80, 96.60)	86.1 (70.50, 95.33)
Percentage of subjects with HI titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.58)	0.0 (0.00, 9.49)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	2.8 (0.07, 14.53)
Percentage of subjects with HI titer ≥1:40 at Day 22 (95% CI)	0.0 (0.00, 10.58)	5.4 (0.66, 18.19)	6.1 (0.74, 20.23)	6.1 (0.74, 20.23)	3.0 (0.08, 15.76)	2.8 (0.07, 14.53)
Percentage of subjects with HI titer ≥1:40 at Day 43 (95% CI)	84.8 (68.10, 94.89)	67.6 (50.21, 81.99)	75.8 (57.74, 88.91)	87.9 (71.80, 96.60)	87.9 (71.80, 96.60)	86.1 (70.50, 95.33)

Source: Table 14.2.1.2 and Table 14.2.1.3.

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; HI = hemagglutination inhibition; N = total number of subjects; n = number of subjects with values in category; PPS = Per Protocol Set.

Note 1: The PPS Immunogenicity is all subjects in the FAS Immunogenicity who: correctly received the vaccine (ie, received the vaccine to which the subject was randomized and at the scheduled time points); provided at least the baseline and one postbaseline blood sample, with evaluable immunogenicity data; have no protocol deviations leading to exclusion as defined prior to unblinding/analysis; and are not excluded due to other reasons defined prior to unblinding or analysis.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Note 3: Seroconversion is defined as either of the following two conditions: subjects with a baseline titer <1:10 by HI assay with a postvaccination titer ≥1:40 OR subjects with baseline titer ≥1:10 by HI assay with a 4-fold or higher increase in postvaccination titer.

GMTs and GMRs for MN Titers (Day 1 to Day 43)

The MN GMT and GMR results of these analyses are adjusted estimates.

Subjects 6 Months to <9 Years of Age

As observed with the HI assay, the **Day 1** (prevaccination) MN titers were very low, bordering on the LLOQ of 10, in the 6 vaccine groups in the overall study population (Table 12).

At **Day 22**:

• In contrast to the HI assay, increases in MN GMTs from Day 1 were observed in all 6 vaccine groups, with the Day 22/Day 1 GMRs ranging from 6.02 to 10.52.

 The Day 22/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 8.85 to 10.52) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 6.02 to 7.66).

At **Day 43:**

• Further increases in MN GMTs were observed across the 6 vaccine groups, with the Day 43/Day 1 GMRs ranging from 102.26 to 168.06.

• The Day 43/Day 1 GMRs also consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 119.78 to 168.06) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 102.26 to 126.71).

Subjects 6 Months to <36 Months of Age

In the 6 months to <36 months age cohort, the MN titers against the homologous H5N1 pandemic influenza strain were very low, bordering on the LLOQ of 10, in the 6 vaccine groups at **Day 1** (Table 12).

At **Day 22:**

• Increases in MN GMTs from Day 1 were observed in all 6 vaccine groups, with the Day 22/Day 1 GMRs ranging from 4.80 to 13.54.

• The Day 22/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 8.09 to 13.54) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 4.80 to 6.52).

At **Day 43:**

• Further increases in MN GMTs were observed in all 6 vaccine groups, with the Day 43/Day 1 GMRs ranging from 122.81 to 214.16.

• The Day 43/Day 1 GMRs consistently tended to be higher for the 100% MF59 formulation than the 50% MF59 formulation for the individual HA antigen doses (1.875 µg HA: 139.62 vs 122.81; 3.75 µg HA: 214.16 vs 180.68; 7.5 µg HA: 164.74 vs 137.36).

Subjects 3 Years to <9 Years of Age

In the 3 years to <9 years age cohort, the MN titers against the homologous H5N1 pandemic influenza strain were very low, bordering on the LLOQ of 10, in the 6 vaccine groups at **Day 1** (Table 12).

At **Day 22:**

• Increases in MN GMTs from Day 1 were observed in all 6 vaccine groups, with the Day 22/Day 1 GMRs ranging from 6.29 to 12.37.

• The Day 22/Day 1 GMRs ranged from 6.29 to 12.37 in the 50% MF59 vaccine groups (Arms A, B, and C) and from 8.00 to 12.18 in the 100% MF59 vaccine groups (Arms D, E, and F).

At **Day 43:**

• Further increases in MN GMTs were observed in all 6 vaccine groups, with the Day 43/Day 1 GMRs ranging from 85.22 to 131.50.

• The Day 43/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 102.76 to 131.50) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 85.22 to 94.64).

• As observed with the HI assay, the increases in MN GMTs tended to be higher in the 6 months to <36 months age cohort (Day 43/Day 1 GMRs, range: 122.81 to 214.16) than in the 3 years to <9 years age cohort (Day 43/Day 1 GMRs, range: 85.22 to 131.50).

Table 12: Pre- and Postvaccination GMTs and GMRs, Overall and by Age Cohort (MN Assay Against the Homologous H5N1 Strain) – As Treated – PPS Immunogenicity

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%)	Arm B (3.75 µg/50%)	Arm C (7.5 µg/50%)	Arm D (1.875 µg/100%)	Arm E (3.75 µg/100%)	Arm F (7.5 µg/100%)
6 Months to <9 Years	**N=67**	**N=71**	**N=67**	**N=66**	**N=69**	**N=67**
MN GMT Day 1 (95% CI)	5.19 (4.9, 5.5)	5.27 (5.0, 5.6)	5.38 (5.1, 5.7)	5.16 (4.9, 5.5)	5.13 (4.9, 5.4)	5.31 (5.0, 5.6)
MN GMT Day 22 (95% CI)	31.42 (24.7, 40.0)	34.83 (27.5, 44.2)	40.61 (31.9, 51.7)	46.08 (36.0, 59.0)	54.66 (42.9, 69.7)	52.81 (41.5, 67.2)
MN GMR Day 22/Day 1 (95% CI)	6.02 (4.7, 7.7)	6.62 (5.2, 8.4)	7.66 (6.0, 9.8)	8.85 (6.9, 11.3)	10.52 (8.2, 13.4)	10.02 (7.9, 12.8)
MN GMT Day 43 (95% CI)	531.04 (424.7, 664.1)	667.86 (536.7, 831.1)	610.37 (488.0, 763.4)	619.44 (494.5, 775.9)	864.91 (693.8, 1078.2)	766.18 (612.6, 958.2)
MN GMR Day 43/Day 1 (95% CI)	102.26 (81.4, 128.5)	126.71 (101.4, 158.4)	113.98 (90.7, 143.2)	119.78 (95.2, 150.7)	168.06 (134.2, 210.5)	144.55 (115.0, 181.6)
6 Months to <36 Months	**N=34**	**N=34**	**N=34**	**N=33**	**N=36**	**N=31**
MN GMT Day 1 (95% CI)	5.00 (4.7, 5.3)	5.00 (4.7, 5.3)	5.26 (4.9, 5.6)	5.21 (4.9, 5.6)	5.10 (4.8, 5.4)	5.29 (4.9, 5.7)
MN GMT Day 22 (95% CI)	29.27 (21.0, 40.8)	33.14 (23.8, 46.2)	24.93 (17.9, 34.7)	45.78 (32.3, 64.8)	69.41 (49.8, 96.7)	42.07 (29.7, 59.6)
MN GMR Day 22/Day 1 (95% CI)	5.76 (4.1, 8.0)	6.52 (4.7, 9.1)	4.80 (3.4, 6.7)	8.84 (6.2, 12.5)	13.54 (9.7, 18.9)	8.09 (5.7, 11.4)
MN GMT Day 43 (95% CI)	618.77 (448.2, 854.3)	910.32 (659.3, 1256.9)	717.83 (520.0, 991.0)	725.06 (522.8, 1005.5)	1094.07 (800.0, 1496.2)	863.94 (616.3, 1211.2)
MN GMR Day 43/Day 1 (95% CI)	122.81 (88.8, 169.9)	180.68 (130.6, 250.0)	137.36 (99.3, 190.0)	139.62 (100.4, 194.1)	214.16 (156.2, 293.6)	164.74 (117.3, 231.4)
3 Years to <9 Years	**N=33**	**N=37**	**N=33**	**N=33**	**N=33**	**N=36**
MN GMT Day 1 (95% CI)	5.38 (4.9, 5.9)	5.54 (5.1, 6.0)	5.49 (5.0, 6.0)	5.11 (4.7, 5.6)	5.16 (4.7, 5.7)	5.35 (4.9, 5.8)
MN GMT Day 22 (95% CI)	33.70 (24.0, 47.4)	36.69 (26.3, 51.1)	66.97 (47.6, 94.2)	46.59 (33.1, 65.6)	42.11 (29.8, 59.6)	65.11 (47.0, 90.2)
MN GMR Day 22/Day 1 (95% CI)	6.29 (4.5, 8.9)	6.73 (4.8, 9.4)	12.37 (8.8, 17.4)	8.90 (6.3, 12.5)	8.00 (5.7, 11.3)	12.18 (8.8, 16.9)
MN GMT Day 43 (95% CI)	458.11 (334.2, 627.9)	495.77 (366.4, 670.9)	518.46 (378.2, 710.8)	527.09 (384.3, 723.0)	680.71 (496.4, 933.4)	670.67 (495.9, 907.0)
MN GMR Day 43/Day 1 (95% CI)	85.22 (61.6, 118.0)	89.57 (65.6, 122.3)	94.64 (68.4, 131.0)	102.76 (74.2, 142.3)	131.50 (95.0, 182.0)	125.44 (91.9, 171.3)

Source: Table 14.2.1.1.8.

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; GMR = geometric mean ratio; GMT = geometric mean titer; MN = microneutralization; N = total number of subjects; n = number of subjects with values in category; PPS = Per Protocol Set.

Note 1: The PPS Immunogenicity is all subjects in the FAS Immunogenicity who: correctly received the vaccine (ie, received the vaccine to which the subject was randomized and at the scheduled time points); provided at least the baseline and one postbaseline blood sample, with evaluable immunogenicity data; have no protocol deviations leading to exclusion as defined prior to unblinding/analysis; and are not excluded due to other reasons defined prior to unblinding or analysis.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Note 3: Adjusted GMTs and GMRs were calculated based on the log-transformed antibody titers at Day 22 and Day 43 using an ANCOVA model that included the log-transformed prevaccination antibody titer, age cohort, and vaccine group.

Note 4: For subjects 6 months to <9 years of age: Arm B: n=69 at Day 22, n=70 at Day 43; Arm D: n=64 at Day 22; Arm E: n=66 at Day 22.For subjects 6 months to <36 months of age: Arm D: n=31 at Day 22, n=34 at Day 22. 3 years to <9 years: Arm B: n=35 at Day 22, n=36 at Day 43; Arm E: n=32 at Day 22.

Percentage of Subjects With MN Seroconversion and Percentage of Subjects with MN Titer ≥1:40 (Day 1 to Day 43)

The percentage of subjects achieving MN seroconversion at Day 22 and Day 43, and the percentage of subjects with MN titer ≥1:40, ≥1:80, and ≥1:160 at Day 1, Day 22, and Day 43, are shown for the overall study population and by age cohort in Table 13.

As observed with the HI assay, because of the very low MN GMTs at Day 1, there were no differences between the percentage of subjects with seroconversion (defined as non-detectable to ≥1:40, or 4-fold increase from a detectable Day 1 titer) and the percentage of subjects with MN titer ≥1:40 at Day 22 or Day 43 in the overall study population or either of the age cohorts. The results for the percentage of subjects with MN titer ≥1:40 are presented below; the same pattern was observed for the percentage of subjects with MN seroconversion.

Subjects 6 Months to <9 Years of Age

MN Titer ≥1:40

At **Day 1**, no subjects had an MN titer ≥1:40 in any of the vaccine groups in the overall study population (Table 13).

At **Day 22**:

• The percentage of subjects with MN titer ≥1:40 ranged from 44.8% to 72.7%.

• The percentages of subjects with MN titer ≥1:40 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 67.2% to 72.7%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 44.8% to 58.2%), suggesting that MF59 content is associated with the magnitude of the immune response.

At **Day 43**, 100% of subjects had an MN titer ≥1:40 across all vaccine groups. Because all subjects had an MN titer ≥1:40, there was no discernible dose pattern for this MN titer cut-off at this time point.

MN Titer ≥1:80
At **Day 1**, no subjects had an MN titer ≥1:80 in any of the vaccine groups in the overall study population (Table 13).
At **Day 22**:
• The percentage of subjects with MN titer ≥1:80 ranged from 22.4% to 40.9%.

• The percentages of subjects with MN titer ≥1:80 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 35.9% to 40.9%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 22.4% to 35.8%).

At **Day 43**, the percentage of subjects with MN titer ≥1:80 ranged from 98.5% to 100% across the vaccine groups. Because of the high percentages of subjects with MN titer ≥1:80, there was no discernible dose pattern for this MN titer cut-off at this time point.
MN Titer ≥1:160
At **Day 1**, no subjects had an MN titer ≥1:160 in any of the vaccine groups in the overall study population (Table 13).
At **Day 22**:
• The percentage of subjects with MN titer ≥1:160 ranged from 5.8% to 16.4%.

• The percentages of subjects with MN titer ≥1:160 ranged from 5.8% to 16.4% in the 50% MF59 vaccine groups (Arms A, B, and C) and from 14.1% to 16.4% in the 100% MF59 vaccine groups (Arms D, E, and F).

At **Day 43**:
• The percentage of subjects with MN titer ≥1:160 ranged from 89.6% to 97.1%.

• The percentages of subjects with MN titer ≥1:160 ranged from 89.6% to 92.9% in the 50% MF59 vaccine groups (Arms A, B, and C) and from 90.9% to 97.1% in the 100% MF59 vaccine groups (Arms D, E, and F).

Subjects 6 Months to <36 Months of Age
MN Titer ≥1:40
In the 6 months to <36 months age cohort, no subjects had an MN titer ≥1:40 at **Day 1** in any of the vaccine groups (Table 13).
At **Day 22**:
• The percentage of subjects with MN titer ≥1:40 ranged from 35.3% to 82.4%.

• The percentages of subjects with MN titer ≥1:40 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 58.1% to 82.4%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 35.3% to 55.9%). At Day 43, 100% of subjects had an MN titer ≥1:40 across all vaccine groups.

MN Titer ≥1:80
In the 6 months to <36 months age cohort, no subjects had an MN titer ≥1:80 at **Day 1** in any of the vaccine groups (Table 13).
At **Day 22**:
• The percentage of subjects with MN titer ≥1:80 ranged from 14.7% to 50.0%.

• The percentages of subjects with MN titer ≥1:80 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 32.3% to 50.0%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 14.7% to 20.6%). At Day 43, the percentage of subjects with MN titer ≥1:80 ranged from 97.0% to 100% across the vaccine groups.

MN Titer ≥1:160
In the 6 months to <36 months age cohort, no subjects had an MN titer ≥1:160 at **Day 1** in any of the vaccine groups (Table 13).
At **Day 22**:
• The percentage of subjects with MN titer ≥1:160 ranged from 2.9% to 26.5%.

• The percentages of subjects with MN titer ≥1:160 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 9.7% to 26.5%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 2.9% to 8.8%).

At **Day 43**:

• The percentage of subjects with MN titer ≥1:160 ranged from 91.2% to 100.0%.

• The percentages of subjects with MN titer ≥1:160 ranged from 91.2% to 97.1% in the 50% MF59 vaccine groups (Arms A, B, and C) and from 93.5% to 100.0% in the 100% MF59 vaccine groups (Arms D, E, and F).

Subjects 3 Years to <9 Years of Age

MN Titer ≥1:40

In the 3 years to <9 years age cohort, no subjects had an MN titer ≥1:40 at **Day 1** in any of the vaccine groups (Table 13).

At **Day 22**:

• The percentage of subjects with MN titer ≥1:40 ranged from 54.5% to 81.8%.

• The percentages of subjects with MN titer ≥1:40 ranged from 54.5% to 81.8% in the 50% MF59 vaccine groups (Arms A, B, and C) and from 62.5% to 77.8% in the 100% MF59 vaccine groups (Arms D, E, and F). At Day 43, 100% of subjects had an MN titer ≥1:40 across all vaccine groups.

MN Titer ≥1:80

In the 3 years to <9 years age cohort, no subjects had an MN titer ≥1:80 at **Day 1** in any of the vaccine groups (Table 13).

At **Day 22**:

• The percentage of subjects with MN titer ≥1:80 ranged from 24.2% to 57.6%.

• The percentages of subjects with MN titer ≥1:80 ranged from 24.2% to 57.6% in the 50% MF59 vaccine groups (Arms A, B, and C) and from 30.3% to 44.4% in the 100% MF59 vaccine groups (Arms D, E, and F). At **Day 43**, 100% of subjects had an MN titer ≥1:80 across all vaccine groups.

MN Titer ≥1:160

In the 3 years to <9 years age cohort, no subjects had an MN titer ≥1:160 at Day 1 in any of the vaccine groups (Table 13).

At Day 22:

• The percentage of subjects with MN titer ≥1:160 ranged from 3.1% to 27.3%.

• The percentages of subjects with MN titer ≥1:160 ranged from 8.6% to 27.3% in the 50% MF59 vaccine groups (Arms A, B, and C) and from 3.1% to 22.2% in the 100% MF59 vaccine groups (Arms D, E, and F).

At **Day 43**:

• The percentage of subjects with MN titer ≥1:160 ranged from 84.8% to 97.2%.

 The percentages of subjects with MN titer ≥1:160 ranged from 84.8% to 88.9% in the 50% MF59 vaccine groups (Arms A, B, and C) and from 84.8% to 97.2% in the 100% MF59 vaccine groups (Arms D, E, and F).

Table 13: Percentage of Subjects With Seroconversion and Percentage of Subjects With MN Titer ≥1:40, ≥1:80, and ≥1:160 Overall and by Age Cohort (MN Assay Against the Homologous H5N1 Strain) – As Treated – PPS Immunogenicity

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%)	Arm B (3.75 µg/50%)	Arm C (7.5 µg/50%)	Arm D (1.875 µg/100%)	Arm E (3.75 µg/100%)	Arm F (7.5 µg/100%)
6 Months to <9 Years	**N=67**	**N=71**	**N=67**	**N=66**	**N=69**	**N=67**
Percentage of subjects with seroconversion at Day 22 (95% CI)	44.8 (32.60, 57.42)	56.5 (44.04, 68.42)	58.2 (45.52, 70.15)	67.2 (54.31, 78.41)	72.7 (60.36, 82.97)	68.7 (56.16, 79.44)
Percentage of subjects with seroconversion at Day 43 (95% CI)	100.0 (94.64, 100.00)	100.0 (94.87, 100.00)	100.0 (94.64, 100.00)	100.0 (94.56, 100.00)	100.0 (94.79, 100.00)	100.0 (94.64, 100.00)
Percentage of subjects with MN titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 5.36)	0.0 (0.00, 5.06)	0.0 (0.00, 5.36)	0.0 (0.00, 5.44)	0.0 (0.00, 5.21)	0.0 (0.00, 5.36)
Percentage of subjects with MN titer ≥1:40 at Day 22 (95% CI)	44.8 (32.60, 57.42)	56.5 (44.04, 68.42)	58.2 (45.52, 70.15)	67.2 (54.31, 78.41)	72.7 (60.36, 82.97)	68.7 (56.16, 79.44)
Percentage of subjects with MN titer ≥1:40 at Day 43 (95% CI)	100.0 (94.64, 100.00)	100.0 (94.87, 100.00)	100.0 (94.64, 100.00)	100.0 (94.56, 100.00)	100.0 (94.79, 100.00)	100.0 (94.64, 100.00)
Percentage of subjects with MN titer ≥1:80 at Day 1 (95% CI)	0.0 (0.00, 5.36)	0.0 (0.00, 5.06)	0.0 (0.00, 5.36)	0.0 (0.00, 5.44)	0.0 (0.00, 5.21)	0.0 (0.00, 5.36)
Percentage of subjects with MN titer ≥1:80 at Day 22 (95% CI)	22.4 (13.11, 34.22)	26.1 (16.25, 38.06)	35.8 (24.47, 48.47)	35.9 (24.32, 48.90)	40.9 (28.95, 53.71)	38.8 (27.14, 51.50)
Percentage of subjects with MN titer ≥1:80 at Day 43 (95% CI)	100.0 (94.64, 100.00)	100.0 (94.87, 100.00)	98.5 (91.96, 99.96)	98.5 (91.84, 99.96)	100.0 (94.79, 100.00)	100.0 (94.64, 100.00)
Percentage of subjects with MN titer ≥1:160 at Day 1 (95% CI)	0.0 (0.00, 5.36)	0.0 (0.00, 5.06)	0.0 (0.00, 5.36)	0.0 (0.00, 5.44)	0.0 (0.00, 5.21)	0.0 (0.00, 5.36)
Percentage of subjects with MN titer ≥1:160 at Day 22 (95% CI)	9.0 (3.36, 18.48)	5.8 (1.60, 14.18)	16.4 (8.49, 27.48)	14.1 (6.64, 25.02)	15.2 (7.51, 26.10)	16.4 (8.49, 27.48)
Percentage of subjects with MN titer ≥1:160 at Day 43 (95% CI)	89.6 (79.65, 95.70)	92.9 (84.11, 97.64)	91.0 (81.52, 96.64)	90.9 (81.26, 96.59)	97.1 (89.92, 99.65)	95.5 (87.47, 99.07)
6 Months to <36 Months	**N=34**	**N=34**	**N=34**	**N=33**	**N=36**	**N=31**
Percentage of subjects with seroconversion at Day 22 (95% CI)	35.3 (19.75, 53.51)	55.9 (37.89, 72.81)	35.3 (19.75, 53.51)	71.0 (51.96, 85.78)	82.4 (65.47, 93.24)	58.1 (39.08, 75.45)
Percentage of subjects with seroconversion at Day 43 (95% CI)	100.0 (89.72, 100.00)	100.0 (89.72, 100.00)	100.0 (89.72, 100.00)	100.0 (89.42, 100.00)	100.0 (90.26, 100.00)	100.0 (88.78, 100.00)
Percentage of subjects with MN titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)	0.0 (0.00, 11.22)
Percentage of subjects with MN titer ≥1:40 at Day 22 (95% CI)	35.3 (19.75, 53.51)	55.9 (37.89, 72.81)	35.3 (19.75, 53.51)	71.0 (51.96, 85.78)	82.4 (65.47, 93.24)	58.1 (39.08, 75.45)
Percentage of subjects with MN titer ≥1:40 at Day 43 (95% CI)	100.0 (89.72, 100.00)	100.0 (89.72, 100.00)	100.0 (89.72, 100.00)	100.0 (89.42, 100.00)	100.0 (90.26, 100.00)	100.0 (88.78, 100.00)
Percentage of subjects with MN titer ≥1:80 at Day 1 (95% CI)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)	0.0 (0.00, 11.22)
Percentage of subjects with MN titer ≥1:80 at Day 22 (95% CI)	20.6 (8.70, 37.90)	20.6 (8.70, 37.90)	14.7 (4.95, 31.06)	41.9 (24.55, 60.92)	50.0 (32.43, 67.57)	32.3 (16.68, 51.37)
Percentage of subjects with MN titer ≥1:80 at Day 43 (95% CI)	100.0 (89.72, 100.00)	100.0 (89.72, 100.00)	97.1 (84.67, 99.93)	97.0 (84.24, 99.92)	100.0 (90.26, 100.00)	100.0 (88.78, 100.00)
Percentage of subjects with MN titer ≥1:160 at Day 1 (95% CI)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)	0.0 (0.00, 11.22)
Percentage of subjects with MN titer ≥1:160 at Day 22 (95% CI)	8.8 (1.86, 23.68)	2.9 (0.07, 15.33)	5.9 (0.72, 19.68)	9.7 (2.04, 25.75)	26.5 (12.88, 44.36)	9.7 (2.04, 25.75)
Percentage of subjects with MN titer ≥1:160 at Day 43 (95% CI)	91.2 (76.32, 98.14)	97.1 (84.67, 99.93)	97.1 (84.67, 99.93)	97.0 (84.24, 99.92)	100.0 (90.26, 100.00)	93.5 (78.58, 99.21)
3 Years to <9 Years	**N=33**	**N=37**	**N=33**	**N=33**	**N=33**	**N=36**
Percentage of subjects with seroconversion at Day 22 (95% CI)	54.5 (36.35, 71.89)	57.1 (39.35, 73.68)	81.8 (64.54, 93.02)	63.6 (45.12, 79.60)	62.5 (43.69, 78.90)	77.8 (60.85, 89.88)
Percentage of subjects with seroconversion at Day 43 (95% CI)	100.0 (89.42, 100.00)	100.0 (90.26, 100.00)	100.0 (89.42, 100.00)	100.0 (89.42, 100.00)	100.0 (89.42, 100.00)	100.0 (90.26, 100.00)
Percentage of subjects with MN titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.58)	0.0 (0.00, 9.49)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)
Percentage of subjects with MN titer ≥1:40 at Day 22 (95% CI)	54.5 (36.35, 71.89)	57.1 (39.35, 73.68)	81.8 (64.54, 93.02)	63.6 (45.12, 79.60)	62.5 (43.69, 78.90)	77.8 (60.85, 89.88)
Percentage of subjects with MN titer ≥1:40 at Day 43 (95% CI)	100.0 (89.42, 100.00)	100.0 (90.26, 100.00)	100.0 (89.42, 100.00)	100.0 (89.42, 100.00)	100.0 (89.42, 100.00)	100.0 (90.26, 100.00)
Percentage of subjects with MN titer ≥1:80 at Day 1 (95% CI)	0.0 (0.00, 10.58)	0.0 (0.00, 9.49)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)
Percentage of subjects with MN titer ≥1:80 at Day 22 (95% CI)	24.2 (11.09, 42.26)	31.4 (16.85, 49.29)	57.6 (39.22, 74.52)	30.3 (15.59, 48.71)	31.3 (16.12, 50.01)	44.4 (27.94, 61.90)
Percentage of subjects with MN titer ≥1:80 at Day 43 (95% CI)	100.0 (89.42, 100.00)	100.0 (90.26, 100.00)	100.0 (89.42, 100.00)	100.0 (89.42, 100.00)	100.0 (89.42, 100.00)	100.0 (90.26, 100.00)
Percentage of subjects with MN titer ≥1:160 at Day 1 (95% CI)	0.0 (0.00, 10.58)	0.0 (0.00, 9.49)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)
Percentage of subjects with MN titer ≥1:160 at Day 22 (95% CI)	9.1 (1.92, 24.33)	8.6 (1.80, 23.06)	27.3 (13.30, 45.52)	18.2 (6.98, 35.46)	3.1 (0.08, 16.22)	22.2 (10.12, 39.15)
Percentage of subjects with MN titer ≥1:160 at Day 43 (95% CI)	87.9 (71.80, 96.60)	88.9 (73.94, 96.89)	84.8 (68.10, 94.89)	84.8 (68.10, 94.89)	93.9 (79.77, 99.26)	97.2 (85.47, 99.93)

Source: Table 14.2.1.2.8, Table 14.2.1.3.8, Table 14.2.1.3.8.1, and Table 14.2.1.3.8.3.

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; MN = microneutralization; N = total number of subjects; n = number of subjects with values in category; PPS = Per Protocol Set.

Note 1: The PPS Immunogenicity is all subjects in the FAS Immunogenicity who: correctly received the vaccine (ie, received the vaccine to which the subject was randomized and at the scheduled time points); provided at least the baseline and one postbaseline blood sample, with evaluable immunogenicity data; have no protocol deviations leading to exclusion as defined prior to unblinding/analysis; and are not excluded due to other reasons defined prior to unblinding or analysis.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Note 3: Seroconversion is defined as either of the following two conditions: subjects with a baseline titer <1:10 by MN assay with a postvaccination titer ≥1:40 OR subjects with baseline titer ≥1:10 by MN assay with a 4-fold or higher increase in postvaccination titer.

Note 4: For subjects 6 months to <9 years of age: Arm B: n=69 at Day 22, n=70 at Day 43; Arm D: n=64 at Day 22; Arm E: n=66 at Day 22. For subjects 6 months to <36 months of age: Arm D: n=31 at Day 22, n=34 at Day 22. For subjects 3 years to <9 years of age: Arm B: n=35 at Day 22, n=36 at Day 43; Arm E: n=32 at Day 22.

The V87_30 study was undertaken to compare in children aged from 6 months to <9 years 6 vaccine formulations containing different HA antigen doses and MF59 adjuvant contents, including the formulation with the licensed dosage for adults of 7.5 µg H5N1 HA antigen in combination with 100% (0.25 mL) MF59, each in a total injection volume of 0.5 mL.

The primary immunogenicity endpoint was assessed by HI and MN assays tested against H5N1 pandemic influenza strain in the total population and by age cohort prior to vaccination (Day 1), at 3 weeks after first vaccination (Day 22) and at 3 weeks after second vaccination (Day 43) and measured by GMT, Day 22/Day 1 and Day 43/Day 1GMRs, as well as seroconversion rate.

As expected, at Day 1 HI antibody response was minimal and similar across the six study vaccination groups (GMT ranging from 5.00 to 5.24). A slight increase as compared to baseline is noted at Day 22 at HI GMTs (GMTs from 5.61 to 6.47) with GMRs similar across vaccination groups and ranging from 1.11 to 1.29. At Day 43 (i.e., 3 weeks after second vaccination) a robust immunogenicity response is elicited as demonstrated by GMTs and GMRs in all 6 vaccination groups, confirming that a 2-dose vaccination schedule is needed.

Day 43 GMT and Day 43/Day1 GMR increases were consistently higher in D, E, F arms characterized by 100% dose of MF59 content (ranging from 122.43 to 123.61 for GMTs and from 24.35 to 24.98 for GMRs) as compared to A, B, C arms conversely characterized by 50% of MF59 content (ranging from 68.06 to 86.70 for GMTs and from 13.77 to 16.38 for GMRs), suggesting that antibody response is enhanced by the MF59 content (50%<100%). This finding was confirmed across age cohorts.

Regarding to antigen dose, no clear effect on immunogenicity was observed, with lower doses achieving similar antibody responses. In vaccine arms D, E, F with 100% MF59 content, HI GMTs at Day 43 (122.43, 123.37, 123.61, respectively) and Day 43/Day 1 GMRs (24.35, 24.98, 23.14, respectively) did not show relevant differences by decreasing antigen dose. Instead, results obtained by MN assay seem to show slightly lower immune responses for Arm D (Day 43 GMT 619.44, Day 43/Day 1 GMR 119.78) compared to Arms E (Day 43 GMT 864.91, Day 43/Day 1 GMR 168.06) and F (Day 43 GMT 766.18, Day 43/Day 1 GMR 144.55). Analysing GMT and GMRs results by age cohorts, as expected younger subjects (6-<36 months) in respect to the older age cohort (3 years -<9 years) seem to show better immunogenicity results, supporting the advantage of using the MF59-adjuvanted in priming an immune response in immunologically naive subjects, like young children.

Regarding seroconversion rate and percentage of subjects with HI titer ≥1:40 (overlapping results were observed as all subjects seroconverting to titers ≥1:40 also had a 4-fold increase from a detectable Day 1 titer), similar results were found with those reported for GMT and GMR response. No relevant increase in HI seroconversion percentages at Day 22 were noted across groups. At Day 43, respectively 90.9%, 87.0%, 86.6% of subjects belonging to arms D, E, and F reached the immunogenicity endpoint, with only 82.1% in arm A, 74.6% in arm B, and 77.6% arm C. MN seroconversion rates at titers ≥1:40, 1≥80, 1≥ 160 confirm the tendency of Arm E (HA antigen 3.75 µg) and F (HA antigen 7.5 µg) to perform better than Arm D (HA antigen 1.875 µg).

Overall, MN assay test results are consistent with those obtained with the HI assay; however, higher antibody titers are observed confirming literature data suggesting the MN functional test (showing neutralizing antibody titres) to be a more sensitive than HI method for detection of antibodies to H5N1 viruses.

Ancillary analyses

Secondary Immunogenicity Endpoints

The persistence of immunological responses to the different doses of antigen and adjuvant contained in the 6 vaccine formulations of aH5N1 was evaluated using HI and MN assays. Blood samples were obtained on Day 1 (prior to the first vaccination) and on Day 202 (6 months after the second vaccination). HI and MN antibody titers on Day 202 were compared with the baseline antibody titers to evaluate persistence of immunogenicity.

The secondary immunogenicity objective was to evaluate in each study vaccine group, by total population and by age cohort, the persistence of antibody responses to the H5N1 vaccine strain 6 months after the second vaccination (Day 202) as measured by HI and MN assays.

Persistence of Antibody Responses at Day 202 (HI Assay)

The GMTs assessed by HI assay against the H5N1 pandemic influenza homologous strain at Day 202 (6 months after the second vaccination), the Day 202/Day 1 GMRs, and the percentages of subjects with seroconversion and HI titer ≥1:40 at Day 202, are shown for the overall study population and by age cohort in Table 14.

There were no differences between the percentage of subjects with seroconversion and the percentage of subjects with HI titer ≥1:40 at Day 202 in the overall study population or either of the age cohorts. The results for the percentage of subjects with HI titer ≥1:40 are described below; the same pattern was observed for the percentage of subjects with HI seroconversion.

Subjects 6 Months to <9 Years of Age

At **Day 202**:

• There was a decrease in HI GMTs in all 6 vaccine groups (range: 7.92 to 13.15; Table 14) compared with the Day 43 HI GMTs (range: 68.06 to 123.61; Table 10).

• The HI GMTs tended to be higher than at Day 1, as indicated by the Day 202/Day 1 GMRs, which ranged from 1.57 to 2.59. The Day 202 HI GMTs (range: 7.92 to 13.15) also tended to be higher than the Day 22 GMTs (range: 5.61 to 6.47; Table 10).

• The Day 202/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 2.02 to 2.59) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 1.57 to 1.78).

• The percentages of subjects with HI titer ≥1:40 consistently tended to be higher than at Day 1, ranging from 10.4% to 25.4%.

• The percentages of subjects with HI titer ≥1:40 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 15.2% to 25.4%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 10.4% to 14.1%).

• The tendency for the Day 202/Day 1 GMRs and percentages of subjects with HI titer ≥1:40 at Day 202 to be higher in the 100% MF59 vaccine groups than the 50% MF59 vaccine groups suggest that MF59 content is associated with the persistence of the immune response.

• There was a consistent trend towards increasing immune responses from the lowest HA antigen/MF59 formulation (Arm A: 1.875 µg HA + 50% MF59) to the highest HA antigen/MF59 formulation (Arm F: 7.5 µg HA + 100% MF59).

Subjects 6 Months to <36 Months of Age

At **Day 202**:

• The HI GMTs tended to be higher than the Day 1 HI GMTs in all 6 vaccine groups, with the Day 202/Day 1 GMRs ranging from 1.79 to 3.81 (Table 14).

• The Day 202/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 2.65 to 3.81) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 1.79 to 2.50).

• The percentages of subjects with HI titer ≥1:40 consistently tended to be higher than at Day 1, ranging from 17.6% to 41.9%.

• The percentages of subjects with HI titer ≥1:40 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 27.3% to 41.9%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 17.6% to 26.5%).

• There was a consistent trend towards increasing immune responses from the lowest HA antigen/MF59 formulation (Arm A: 1.875 µg HA + 50% MF59) to the highest HA antigen/MF59 formulation (Arm F: 7.5 µg HA + 100% MF59).

Subjects 3 Years to <9 Years of Age

At **Day 202**:

• The HI GMTs tended to be higher than the Day 1 HI GMTs in all 6 vaccine groups, with the Day 202/Day 1 GMRs ranging from 1.28 to 1.74 (Table 14).

• The Day 202/Day 1 GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 1.54 to 1.74) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 1.28 to 1.38).

• The percentages of subjects with HI titer ≥1:40 ranged from 0.0% to 11.1%.

• The percentages of subjects with HI titer ≥1:40 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 3.0% to 11.1%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 0.0% to 3.0%).

• The trend towards increasing immune responses from the lowest HA antigen/MF59 formulation (Arm A: 1.875 µg HA + 50% MF59) to the highest HA antigen/MF59 formulation (Arm F: 7.5 µg HA + 100% MF59) was less evident.

• The Day 202/Day 1 GMRs tended to be higher in the vaccine groups in the 6 months to <36 months age cohort (1.79 to 3.81) than in the 3 years to <9 years age cohort (1.28 to 1.74).

• The percentages of subjects with HI titer ≥1:40 tended to be higher in the vaccine groups in the 6 months to <36 months age cohort (17.6% to 41.9%) than in the 3 years to <9 years age cohort (0.0% to 11.1%).

Table 14: Persistence of Antibody Responses on Day 202 – GMTs and GMRs, Percentage of Subjects With Seroconversion, and Percentage of Subjects With HI Titer ≥1:40, Overall and by Age Cohort (HI Assay Against the Homologous H5N1 Strain) – As Treated – PPS Immunogenicity

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%)	Arm B (3.75 µg/50%)	Arm C (7.5 µg/50%)	Arm D (1.875 µg/100%)	Arm E (3.75 µg/100%)	Arm F (7.5 µg/100%)
6 Months to <9 Years	**N=67**	**N=71**	**N=67**	**N=66**	**N=69**	**N=67**
HI GMT Day 1 (95% CI)	5.05 (4.8, 5.3)	5.00 (4.8, 5.2)	5.21 (5.0, 5.4)	5.05 (4.8, 5.3)	5.00 (4.8, 5.2)	5.24 (5.0, 5.5)
HI GMT Day 202 (95% CI)	7.92 (6.3, 9.9)	8.90 (7.2, 11.0)	8.81 (7.1, 11.0)	10.19 (8.2, 12.7)	12.90 (10.4, 16.1)	13.15 (10.5, 16.4)
HI GMR Day 202/Day 1 (95% CI)	1.57 (1.3, 2.0)	1.78 (1.4, 2.2)	1.69 (1.3, 2.1)	2.02 (1.6, 2.5)	2.59 (2.1, 3.2)	2.50 (2.0, 3.1)
Percentage of subjects with seroconversion at Day 202 (95% CI)	10.4 (4.30, 20.35)	14.1 (6.97, 24.38)	11.9 (5.30, 22.18)	15.2 (7.51, 26.10)	21.7 (12.71, 33.31)	25.4 (15.53, 37.49)
Percentage of subjects with HI titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 5.36)	0.0 (0.00, 5.06)	0.0 (0.00, 5.36)	0.0 (0.00, 5.44)	0.0 (0.00, 5.21)	1.5 (0.04, 8.04)
Percentage of subjects with HI titer ≥1:40 at Day 202 (95% CI)	10.4 (4.30, 20.35)	14.1 (6.97, 24.38)	11.9 (5.30, 22.18)	15.2 (7.51, 26.10)	21.7 (12.71, 33.31)	25.4 (15.53, 37.49)
6 Months to <36 Months	**N=34**	**N=34**	**N=34**	**N=33**	**N=36**	**N=31**
HI GMT Day 1 (95% CI)	5.10 (4.9, 5.3)	5.00 (4.8, 5.2)	5.42 (5.2, 5.7)	5.11 (4.9, 5.3)	5.00 (4.8, 5.2)	5.00 (4.8, 5.2)
HI GMT Day 202 (95% CI)	9.11 (6.3, 13.3)	12.57 (8.6, 18.3)	11.60 (7.9, 17.0)	13.55 (9.3, 19.8)	19.12 (13.3, 27.6)	19.00 (12.8, 28.2)
HI GMR Day 202/Day 1 (95% CI)	1.79 (1.2, 2.6)	2.50 (1.7, 3.6)	2.17 (1.5, 3.2)	2.65 (1.8, 3.9)	3.81 (2.6, 5.5)	3.78 (2.5, 5.6)
Percentage of subjects with seroconversion at Day 202 (95% CI)	17.6 (6.76, 34.53)	26.5 (12.88, 44.36)	23.5 (10.75, 41.17)	27.3 (13.30, 45.52)	33.3 (18.56, 50.97)	41.9 (24.55, 60.92)
Percentage of subjects with HI titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)	0.0 (0.00, 11.22)
Percentage of subjects with HI titer ≥1:40 at Day 202 (95% CI)	17.6 (6.76, 34.53)	26.5 (12.88, 44.36)	23.5 (10.75, 41.17)	27.3 (13.30, 45.52)	33.3 (18.56, 50.97)	41.9 (24.55, 60.92)
3 Years to <9 Years	**N=33**	**N=37**	**N=33**	**N=33**	**N=33**	**N=36**
HI GMT Day 1 (95% CI)	5.00 (4.6, 5.4)	5.00 (4.7, 5.4)	5.00 (4.6, 5.4)	5.00 (4.6, 5.4)	5.00 (4.6, 5.4)	5.45 (5.1, 5.9)
HI GMT Day 202 (95% CI)	6.90 (5.4, 8.8)	6.36 (5.1, 8.0)	6.55 (5.2, 8.3)	7.66 (6.0, 9.7)	8.69 (6.8, 11.0)	9.30 (7.4, 11.7)
HI GMR Day 202/Day 1 (95% CI)	1.38 (1.1, 1.8)	1.28 (1.0, 1.6)	1.31 (1.0, 1.7)	1.54 (1.2, 2.0)	1.74 (1.4, 2.2)	1.68 (1.3, 2.1)
Percentage of subjects with seroconversion at Day 202 (95% CI)	3.0 (0.08, 15.76)	2.7 (0.07, 14.16)	0.0 (0.00, 10.58)	3.0 (0.08, 15.76)	9.1 (1.92, 24.33)	11.1 (3.11, 26.06)
Percentage of subjects with HI titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.58)	0.0 (0.00, 9.49)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	2.8 (0.07, 14.53)
Percentage of subjects with HI titer ≥1:40 at Day 202 (95% CI)	3.0 (0.08, 15.76)	2.7 (0.07, 14.16)	0.0 (0.00, 10.58)	3.0 (0.08, 15.76)	9.1 (1.92, 24.33)	11.1 (3.11, 26.06)

Source: Table 14.2.1.1, Table 14.2.1.2, and Table 14.2.1.3.

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; FAS = Full Analysis Set; HI = hemagglutination inhibition; N = total number of subjects; n = number of subjects with values in category; PPS = Per Protocol Set.

Note 1: The PPS Immunogenicity is all subjects in the FAS Immunogenicity who: correctly received the vaccine (ie, received the vaccine to which the subject was randomized and at the scheduled time points); provided at least the baseline and one postbaseline blood sample, with evaluable immunogenicity data; have no protocol deviations leading to exclusion as defined prior to unblinding/analysis; and are not excluded due to other reasons defined prior to unblinding or analysis.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Note 3: Adjusted GMTs and GMRs were calculated based on the log-transformed antibody titers at Day 22 and Day 43 using an ANCOVA model that included the log-transformed prevaccination antibody titer, age cohort, and vaccine group.

Note 4: Seroconversion is defined as either of the following two conditions: subjects with a baseline titer <1:10 by HI assay with a postvaccination titer ≥1:40 OR subjects with baseline titer ≥1:10 by HI assay with a 4-fold or higher increase in postvaccination titer.

Persistence of Antibody Responses at Day 202 (MN Assay)

The GMTs assessed by MN assay against the H5N1 pandemic influenza homologous strain at Day 202, the Day 202/Day 1 GMRs and the percentages of subjects with seroconversion and MN titer ≥1:40, ≥1:80, and ≥1:160 are shown for the overall study population and by age cohort in Table 15.

There were few differences between the percentage of subjects with seroconversion and the percentage of subjects with MN titer ≥1:40 at Day 202 in the overall study population or either of the age cohorts. The results for the percentage of subjects with MN titer ≥1:40 are described below; a similar pattern was observed for the percentage of subjects with MN seroconversion.

Subjects 6 Months to <9 Years of Age

At **Day 202**:

• There was a decrease in MN GMTs in all 6 vaccine groups (range: 113.24 to 195.57; Table 15) compared with the Day 43 MN GMTs (range: 531.04 to 864.91; Table 12).

• The MN GMTs tended to be higher than at Day 1, as indicated by the Day 202/Day 1 GMRs, which ranged from 21.77 to 36.95. The Day 202 MN GMTs (range: 113.24 to 195.57) also tended to be higher than the Day 22 MN GMTs (range: 31.42 to 54.66; Table 12).

• The Day 202/Day 1 MN GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 29.04 to 36.95) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 21.77 to 27.94).

• The percentage of subjects with MN titer ≥1:40 ranged from 95.5% to 100.0%, with MN titer ≥1:80 ranged from 76.1% to 94.2%, and with MN titer ≥1:160 ranged from 44.8% to 68.2%.

• Because of the high percentages of subjects with MN titer ≥1:40, there was no discernible dose pattern with respect to MF59 content or trend for increasing immune response from lowest to highest HA antigen/MF59 formulation for this MN titer cut-off.

• The percentages of subjects with MN titer ≥1:80 and ≥1:160 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 87.9% to 94.2% and 62.1% to respectively) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 76.1% to 88.1% and 44.8% to 54.9%, respectively). • The tendency for the Day 202/Day 1 GMRs and percentages of subjects with MN titer ≥ 1:80 and ≥1:160 at Day 202 to be higher in the 100% MF59 vaccine groups than the 50% MF59 vaccine groups suggest that MF59 content is associated with the persistence of the immune response.

• There was a consistent trend towards increasing immune responses from the lowest HA antigen/MF59 formulation (Arm A: 1.875 µg HA + 50% MF59) to the highest HA antigen/MF59 formulation (Arm F: 7.5 µg HA + 100% MF59).

Subjects 6 Months to <36 Months of Age

At **Day 202**:

• The MN GMTs tended to be higher than the **Day 1** MN GMTs in all 6 vaccine groups, with the Day 202/Day 1 GMRs ranging from 28.49 to 51.56 (Table 15).

• The Day 202/Day 1 GMRs consistently tended to be higher for the 100% MF59 formulation than the 50% MF59 formulation for the individual HA antigen doses (1.875 µg HA: 33.68 vs 28.49; 3.75 µg HA: 47.95 vs 42.91; 7.5 µg HA: 51.56 vs 33.76).

• The percentage of subjects with MN titer ≥1:40 ranged from 97.0% to 100.0%, with MN titer ≥1:80 ranged from 85.3% to 96.8%, and with MN titer ≥1:160 ranged from 58.8% to 83.9%.

• The percentages of subjects with MN titer ≥1:80 and ≥1:160 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 90.9% to 96.8% and 72.7% to 83.9%, respectively) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 85.3% to 94.1% and 58.8% to 76.5%, respectively).

• There was a consistent trend towards increasing immune responses from the lowest HA antigen/MF59 formulation (Arm A: 1.875 µg HA + 50% MF59) to the highest HA antigen/MF59 formulation (Arm F: 7.5 µg HA + 100% MF59).

Subjects 3 Years to <9 Years of Age

At **Day 202**:

• The MN GMTs tended to be higher than the Day 1 MN GMTs in all 6 vaccine groups, with the Day 202/Day 1 GMRs ranging from 16.64 to 26.63 (Table 15).

• The Day 202/Day 1 MN GMRs consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 25.04 to 26.63) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 16.64 to 22.38).

• The percentage of subjects with MN titer ≥1:40 ranged from 93.9% to 100.0%, with MN titer ≥1:80 ranged from 66.7% to 93.9%, and with MN titer ≥1:160 ranged from 30.3% to 54.3%.

• The percentages of subjects with MN titer ≥1:80 and ≥1:160 consistently tended to be higher in the 100% MF59 vaccine groups (Arms D, E, and F, range: 84.8% to 93.9% and 51.5% to 54.3%) than the 50% MF59 vaccine groups (Arms A, B, and C, range: 66.7% to 84.8% and 30.3% to 39.4%).

• There was a consistent trend towards increasing immune responses from the lowest HA antigen/MF59 formulation (Arm A: 1.875 µg HA + 50% MF59) to the highest HA antigen/MF59 formulation (Arm F: 7.5 µg HA + 100% MF59).

• The Day 202/Day 1 GMRs tended to be higher in the vaccine groups in the 6 months to <36 months age cohort (28.49 to 51.56) than in the 3 years to <9 years age cohort (16.64 to 26.63).

• The percentages of subjects with MN titer ≥1:160 tended to be higher in the vaccine groups in the 6 months to <36 months age cohort (58.8% to 83.9%) than in the 3 years to <9 years age cohort (30.3% to 54.3%).

Table 15: Persistence of Antibody Responses on Day 202 – GMTs and GMRs, Percentage of Subjects With Seroconversion, and Percentage of Subjects With MN Titer ≥1:40, Overall and by Age Cohort (MN Assay Against the Homologous H5N1 Strain) – As Treated – PPS Immunogenicity

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%)	Arm B (3.75 µg/50%)	Arm C (7.5 µg/50%)	Arm D (1.875 µg/100%)	Arm E (3.75 µg/100%)	Arm F (7.5 µg/100%)
6 Months to <9 Years	**N=67**	**N=71**	**N=67**	**N=66**	**N=69**	**N=67**
MN GMT Day 1 (95% CI)	5.19 (4.9, 5.5)	5.27 (5.0, 5.6)	5.38 (5.1, 5.7)	5.16 (4.9, 5.5)	5.13 (4.9, 5.4)	5.31 (5.0, 5.6)
MN GMT Day 202 (95% CI)	113.24 (94.7, 135.4)	146.98 (123.6, 174.8)	146.41 (122.4, 175.1)	150.56 (125.7, 180.3)	183.15 (153.6, 218.4)	195.57 (163.3, 234.2)
MN GMR Day 202/Day 1 (95% CI)	21.77 (18.1, 26.1)	27.94 (23.4, 33.4)	27.45 (22.9, 33.0)	29.04 (24.2, 34.9)	35.47 (29.6, 42.5)	36.95 (30.7, 44.4)
Percentage of subjects with seroconversion at Day 202 (95% CI)	95.5 (87.47, 99.07)	97.2 (90.19, 99.66)	100.0 (94.64, 100.00)	97.0 (89.48, 99.63)	98.6 (92.19, 99.96)	97.0 (89.48, 99.63)
Percentage of subjects with MN titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 5.36)	0.0 (0.00, 5.06)	0.0 (0.00, 5.36)	0.0 (0.00, 5.44)	0.0 (0.00, 5.21)	0.0 (0.00, 5.36)
Percentage of subjects with MN titer ≥1:40 at Day 202 (95% CI)	95.5 (87.47, 99.07)	98.6 (92.40, 99.96)	100.0 (94.64, 100.00)	97.0 (89.48, 99.63)	98.6 (92.19, 99.96)	98.5 (91.84, 99.96)
Percentage of subjects with MN titer ≥1:80 at Day 202 (95% CI)	76.1 (64.14, 85.69)	81.7 (70.73, 89.87)	88.1 (77.82, 94.70)	87.9 (77.51, 94.62)	94.2 (85.82, 98.40)	90.9 (81.26, 96.59)
Percentage of subjects with MN titer ≥1:160 at Day 202 (95% CI)	44.8 (32.60, 57.42)	54.9 (42.66, 66.77)	52.2 (39.67, 64.60)	62.1 (49.34, 73.78)	63.8 (51.31, 75.01)	68.2 (55.56, 79.11)
6 Months to <36 Months	**N=34**	**N=34**	**N=34**	**N=33**	**N=36**	**N=31**
MN GMT Day 1 (95% CI)	5.00 (4.7, 5.3)	5.00 (4.7, 5.3)	5.26 (4.9, 5.6)	5.21 (4.9, 5.6)	5.10 (4.8, 5.4)	5.29 (4.9, 5.7)
MN GMT Day 202 (95% CI)	144.60 (111.8, 187.0)	217.84 (168.4, 281.7)	175.31 (135.6, 226.7)	174.21 (134.2, 226.1)	245.52 (191.3, 315.1)	268.31 (205.0, 351.3)
MN GMR Day 202/Day 1 (95% CI)	28.49 (22.0, 36.9)	42.91 (33.2, 55.5)	33.76 (26.1, 43.7)	33.68 (25.9, 43.7)	47.95 (37.3, 61.6)	51.56 (39.4, 67.5)
Percentage of subjects with seroconversion at Day 202 (95% CI)	97.1 (84.67, 99.93)	100.0 (89.72, 100.00)	100.0 (89.72, 100.00)	97.0 (84.24, 99.92)	100.0 (90.26, 100.00)	100.0 (88.78, 100.00)
Percentage of subjects with MN titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.28)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)	0.0 (0.00, 11.22)
Percentage of subjects with MN titer ≥1:40 at Day 202 (95% CI)	97.1 (84.67, 99.93)	100.0 (89.72, 100.00)	100.0 (89.72, 100.00)	97.0 (84.24, 99.92)	100.0 (90.26, 100.00)	100.0 (88.78, 100.00)
Percentage of subjects with MN titer ≥1:80 at Day 202 (95% CI)	85.3 (68.94, 95.05)	94.1 (80.32, 99.28)	91.2 (76.32, 98.14)	90.9 (75.67, 98.08)	94.4 (81.34, 99.32)	96.8 (83.30, 99.92)
Percentage of subjects with MN titer ≥1:160 at Day 202 (95% CI)	58.8 (40.70, 75.35)	76.5 (58.83, 89.25)	64.7 (46.49, 80.25)	72.7 (54.48, 86.70)	75.0 (57.80, 87.88)	83.9 (66.27, 94.55)
3 Years to <9 Years	**N=33**	**N=37**	**N=33**	**N=33**	**N=33**	**N=36**
MN GMT Day 1 (95% CI)	5.38 (4.9, 5.9)	5.54 (5.1, 6.0)	5.49 (5.0, 6.0)	5.11 (4.7, 5.6)	5.16 (4.7, 5.7)	5.35 (4.9, 5.8)
MN GMT Day 202 (95% CI)	89.38 (69.6, 114.8)	101.19 (79.8, 128.2)	122.19 (95.1, 157.0)	129.11 (100.4, 165.9)	136.08 (105.9, 174.9)	142.59 (111.8, 181.8)
MN GMR Day 202/Day 1 (95% CI)	16.64 (12.8, 21.6)	18.41 (14.4, 23.5)	22.38 (17.3, 29.0)	25.04 (19.3, 32.5)	26.18 (20.2, 34.0)	26.63 (20.7, 34.3)
Percentage of subjects with seroconversion at Day 202 (95% CI)	93.9 (79.77, 99.26)	94.6 (81.81, 99.34)	100.0 (89.42, 100.00)	97.0 (84.24, 99.92)	97.0 (84.24, 99.92)	94.3 (80.84, 99.30)
Percentage of subjects with MN titer ≥1:40 at Day 1 (95% CI)	0.0 (0.00, 10.58)	0.0 (0.00, 9.49)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 10.58)	0.0 (0.00, 9.74)
Percentage of subjects with MN titer ≥1:40 at Day 202 (95% CI)	93.9 (79.77, 99.26)	97.3 (85.84, 99.93)	100.0 (89.42, 100.00)	97.0 (84.24, 99.92)	97.0 (84.24, 99.92)	97.1 (85.08, 99.93)
Percentage of subjects with MN titer ≥1:80 at Day 202 (95% CI)	66.7 (48.17, 82.04)	70.3 (53.02, 84.13)	84.8 (68.10, 94.89)	84.8 (68.10, 94.89)	93.9 (79.77, 99.26)	85.7 (69.74, 95.19)
Percentage of subjects with MN titer ≥1:160 at Day 202 (95% CI)	30.3 (15.59, 48.71)	35.1 (20.21, 52.54)	39.4 (22.91, 57.86)	51.5 (33.54, 69.20)	51.5 (33.54, 69.20)	54.3 (36.65, 71.17)

Source: Table 14.2.1.1.8, Table 14.2.1.2.8, Table 14.2.1.3.8, Table 14.2.1.3.8.1, and Table 14.2.1.3.8.3.

Secondary immunogenicity endpoints looked at persistence of immunological responses to the different vaccine formulations by comparing response as measured by HI and MN antibody titers on Day 202 (i.e., 6 months after second vaccination). Analysis was carried out in the total population and by age cohort.

At Day 202, HI and MN assays both showed GMTs and GMRs against the H5N1 pandemic influenza homologous strain that are decreased in respect to Day 43 for all vaccination groups. However, Day 202/Day 1 GMRs were increased in respect to baseline and superior in the 100% MF59 vaccine groups

(Arms D, E, F) than in the 50% MF59 groups (Arms A, B, C), suggesting that higher adjuvant content is associated with longer persistence of antibody response; this was confirmed when analysing data by age cohorts.

The highest percentages of subjects with an antibody titre ≥1:40 (or seroconversion) at 6 months after second vaccine dose by both HI and MN assays was found in Arm F (HA antigen-adjuvant ratio 7.5 µg/100% MF59) with, respectively, 25.4% and 98.5% of the study population. While in respect to Arm F, lower HI seroconversion rates were found in Arm D (15.2%), Arm E performed similarly (21.7%) in the overall population. Consistent differences across Arms D-F were reported for the two age cohorts, that however displayed a superior immune response in younger children (Arm D 27.1% versus Arm E 33.3% and Arm F 41.9%) than in older children (Arm D 3.0% versus Arm E 9.1% and Arm F 11.1%).

Conclusively, all immunogenicity endpoints confirmed that a higher adjuvant content is needed to elicit a greater antibody response across age cohorts. Among vaccine formulations with 100% MF59, the adult and half adult dose showed similar antibody responses, while for the smaller antigen formulation lower immune responses were reported; this was even more evident in children aged between 3-8 years of age. Therefore, the proposed dose for the paediatric population, that is the same as for adults (7.5 µg+100% MF59), sounds reasonable. However, a lower antigen dose (3.75 µg) in respect to the licensed adult dosage could also be considered.

Reverse Cumulative Distribution Curves

The immune response profiles for the H5N1 pandemic influenza homologous strain at Day 22 and Day 43 in the 6 vaccine groups in the 6 months to <36 months age cohort and the 3 years to <9 years age cohort based on HI titers are shown graphically using reverse cumulative distribution (RCD) curves.

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.

HI assay

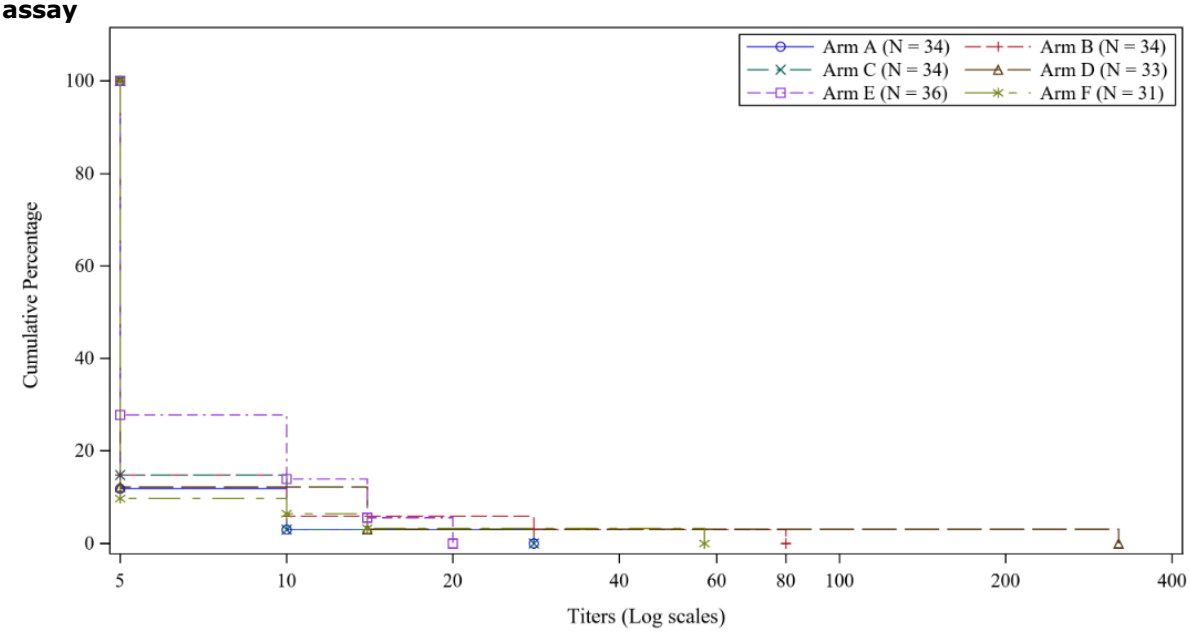


Figure 2: Reverse Cumulative Distribution Curves of HI Antibody Titers for the H5N1 Pandemic Influenza Homologous Strain by Vaccine Group on Day 22 in Subjects 6 Months to<36 Months – PPS Immunogenicity

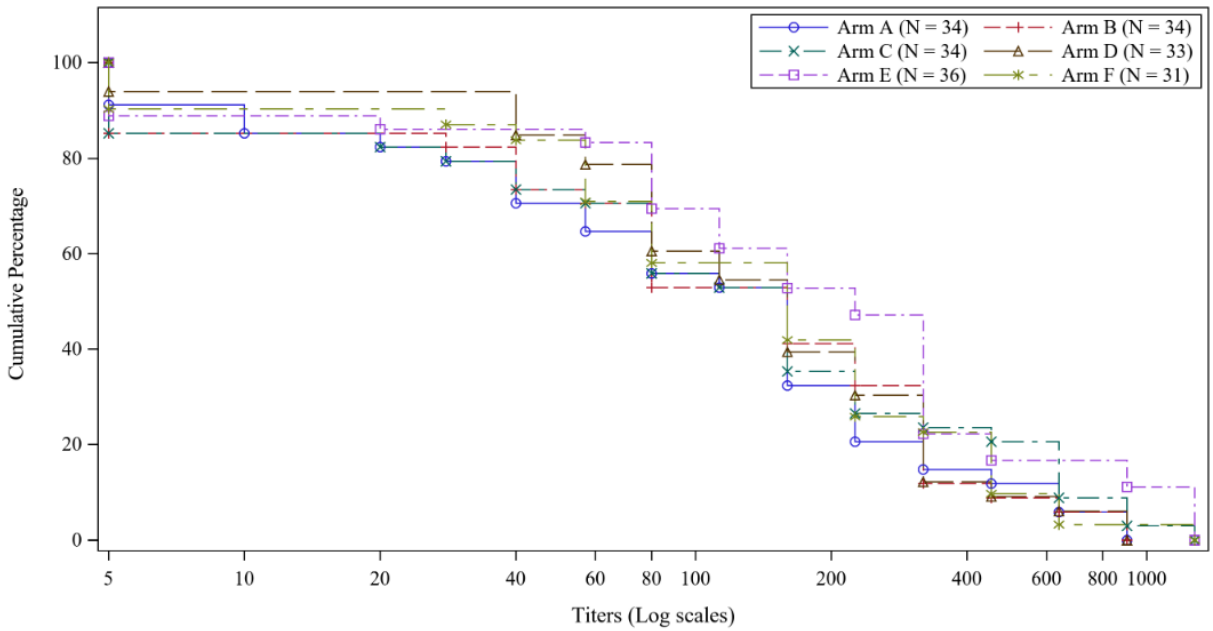


Figure 3: Reverse Cumulative Distribution Curves of HI Antibody Titers for the H5N1 Pandemic Influenza Homologous Strain by Vaccine Group on Day 43 in Subjects 6 Months to <36 Months – PPS Immunogenicity

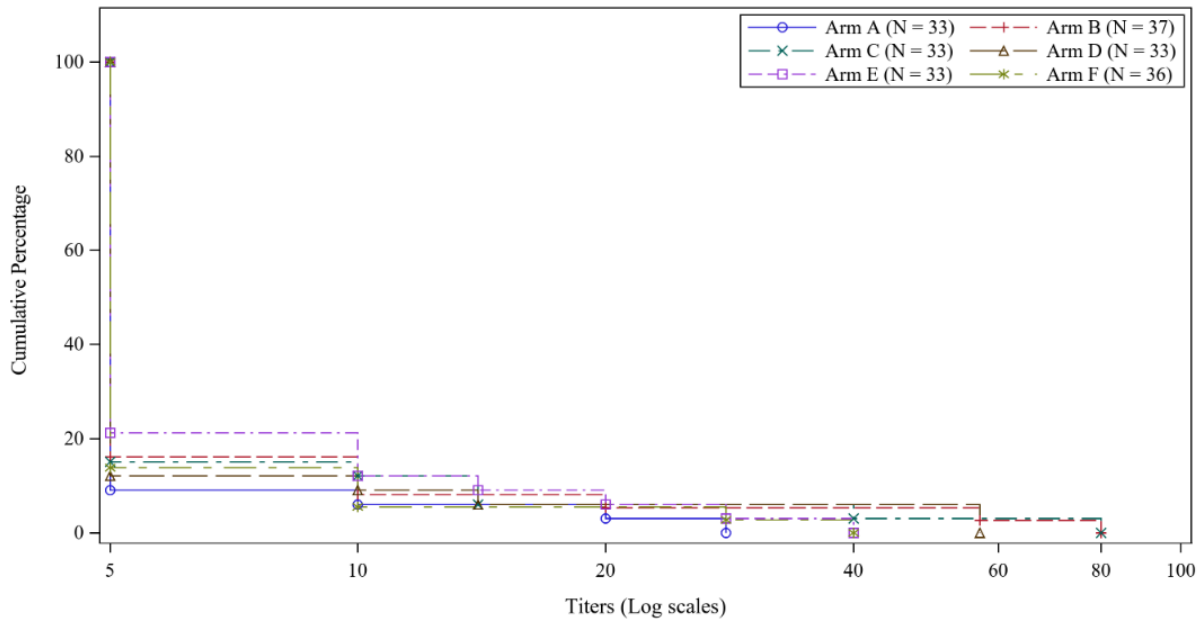


Figure 4: Reverse Cumulative Distribution Curves of HI Antibody Titers for the H5N1 Pandemic Influenza Homologous Strain by Vaccine Group on Day 22 in Subjects 3 Years to <9 Years – PPS Immunogenicity

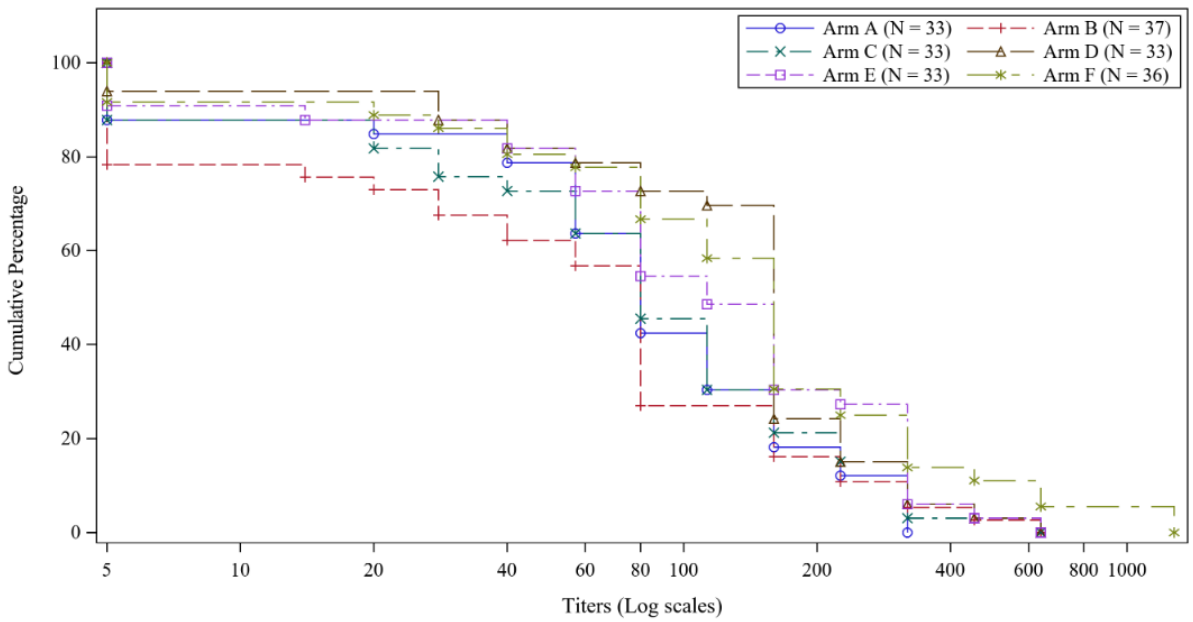


Figure 5: Reverse Cumulative Distribution Curves of HI Antibody Titers for the H5N1 Pandemic Influenza Homologous Strain by Vaccine Group on Day 43 in Subjects 3 Years to <9 Years – PPS Immunogenicity

RCD curves using MN assay are not reported, similar results to that of HI assay have been obtained.

Overall, RCD curves for the H5N1 pandemic influenza homologous strain based on HI titers were similar across the 6 vaccine groups at Day 22 and Day 43 in both age cohorts. Comparison of results at Day 43 with those at Day 22 suggests that MF59 content is associated with the magnitude of the immune response.

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 16: Summary of Efficacy for Study V87_30

Title: A Phase 2, Randomized, Observer-Blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Several Doses of Antigen and MF59 Adjuvant Content in a Monovalent H5N1 Pandemic Influenza Vaccine in Healthy Paediatric Subjects 6 Months to < 9 Years of Age		
Study identifier	Paediatric Study V87_30	
Design	Phase 2, randomized, observer-blind, multicentre study evaluating the immunogenicity and safety of 6 aH5N1 vaccine formulations in healthy children aged 6 months to <9 years	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Dec 2020 – April 2022 not applicable not applicable
Hypothesis	No formal (null) hypothesis was included	
Treatments groups	Group A	1.875 µg HA/50% MF59, 12 months, n=69
	Group B	3.75 µg HA/50% MF59, 12 months, n=72
	Group C	7.5 µg HA/50% MF59, 12 months, n=70
	Group D	1.875 µg HA/100% MF59, 12 months, n=70
	Group E	3.75 µg HA/100% MF59, 12 months, n=69

Eligible subjects were stratified by age at the time of enrolment into one of two age cohorts: 6 months to <36 months of age and 3 years to <9 years of age.	Group F		7.5 µg HA/100% MF59, 12 months, n=70
Endpoints and definitions			
	Primary Immunogenicity Endpoints	GMTs at Day 43	GMTs on Day 43 (3 weeks after the second vaccination) as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain
		Day 43/Day 1 GMR	GMRs calculated as follows: Day 43/Day 1 as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain
		Seroconversion on Day 43	Percentage of subjects achieving seroconversion (non-detectable to ≥ 1:40, or 4-fold increase from a detectable Day 1 titer) on Day 43
	Secondary Immunogenicity Endpoint	GMTs at Day 202	GMTs on Day 202 as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain
		GMR Day 202/Day 1	GMRs calculated as follows: Day 202/Day 1 as determined by HI and MN assays
		Seroconversion on Day 202	Percentage of subjects achieving seroconversion (non-detectable to ≥1:40, or 4-fold increase from a detectable Day 1 titer) on Day 202 by HI and MN
Database lock	15 April 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	As Treated – PPS Immunogenicity		

Descriptive statistics and estimate variability	**Treatment group (6 mo-<9 yrs)**	**A**	**B**	**C**	**D**	**E**	**F**
	Number of subjects	N=67	N=71	N=67	N=66	N=69	N=67
	Primary immunogenicity endpoint						
	HI GMT Day 43 (95% CI)	81.10 (58.3, 112.8)	68.06 (49.4, 93.8)	86.70 (62.3, 120.7)	**122.43** (87.8, 170.7)	**123.37** (89.1, 170.8)	**123.61** (88.8, 172.1)
	HI GMR Day 43/Day 1 (95% CI)	16.14 (11.5, 22.6)	13.77 (9.9, 19.1)	16.38 (11.7, 23.0)	**24.35** (17.3, 34.2)	**24.98** (17.9, 34.8)	**23.14** (16.5, 32.4)
	Percentage of subjects with HI seroconversion at Day 43 (95% CI)	82.1 (70.80-90.39)	74.6 (62.92, 84.23)	77.6 (65.78, 86.89)	**90.9** (81.26, 96.59)	**87.0** (76.68, 93.86)	**86.6** (76.03, 93.67)
	MN GMT Day 43 (95% CI)	531.04 (424.7, 664.1)	667.86 (536.7, 831.1)	610.37 (488.0, 763.4)	**619.44** (494.5, 775.9)	**864.91** (693.8, 1078.2)	**766.18** (612.6, 958.2)
	MN GMR Day 43/Day 1 (95% CI)	102.26 (81.4, 128.5)	126.71 (101.4, 158.4)	113.98 (90.7, 143.2)	**119.78** (95.2, 150.7)	**168.06** (134.2, 210.5)	**144.55** (115.0, 181.6)
	Percentage of subjects with MN seroconversion at Day 43 (95% CI)	100.0 (94.64, 100.00)	100.0 (94.87, 100.00)	100.0 (94.64, 100.00)	**100.0** (94.56, 100.00)	**100.0** (94.79, 100.00)	**100.0** (94.64, 100.00)
	Secondary immunogenicity endpoint						
	HI GMT Day 202 (95% CI)	7.92 (6.3, 9.9)	8.90 (7.2, 11.0)	8.81 (7.1, 11.0)	**10.19** (8.2, 12.7)	**12.90** (10.4, 16.1)	**13.15** (10.5, 16.4)

	HI GMR Day 202/Day 1 (95% CI)	1.57 (1.3, 2.0)	1.78 (1.4, 2.2)	1.69 (1.3, 2.1)	**2.02** (1.6, 2.5)	**2.59** (2.1, 3.2)	**2.50** (2.0, 3.1)
	HI percentage of subjects with seroconversion at Day 202 (95% CI)	10.4 (4.30, 20.35)	14.1 (6.97, 24.38)	11.9 (5.30, 22.18)	**15.2** (7.51, 26.10)	**21.7** (12.71, 33.31)	**25.4** (15.53, 37.49)
	MN GMT Day 202 (95% CI)	113.24 (94.7, 135.4)	146.98 (123.6, 174.8)	146.41 (122.4, 175.1)	**150.56** (125.7, 180.3)	**183.15** (153.6, 218.4)	**195.57** (163.3, 234.2)
	MN GMR Day 202/Day 1 (95% CI)	21.77 (18.1, 26.1)	27.94 (23.4, 33.4)	27.45 (22.9, 33.0)	**29.04** (24.2, 34.9)	**35.47** (29.6, 42.5)	**36.95** (30.7, 44.4)
	MN percentage of subjects with seroconversion at Day 202 (95% CI)	95.5 (87.47, 99.07)	97.2 (90.19, 99.66)	100.0 (94.64, 100.00)	**97.0** (89.48, 99.63)	**98.6** (92.19, 99.96)	**97** (89.48, 99.63)

2.4.2. Discussion on clinical efficacy

In a pandemic situation, children may be very vulnerable to infection and so constitute a special target group for vaccination.Design and conduct of clinical studies.

Consistent with the relevant GL EMEA/CPMP/VEG/4717/2003 in this application the MAH has submitted the core pandemic dossier including immunogenicity and safety data obtained with the 2-dose regimen of the mock-up vaccine containing the influenza virus to which most of the study population has no detectable immunity. As expected for pre-pandemic phase applications, no efficacy data is provided.

Design

Study V87_30 was a Phase 2, randomized, observer-blind, multicenter study conducted to evaluate the immunogenicity and safety of several doses of H5N1 pandemic influenza vaccine with decreased doses of H5N1 HA antigen and/or adjuvant in respect of licenced formulation administered as 2 vaccinations given 3 weeks apart in healthy paediatric subjects 6 months to <9 years of age. The monovalent MF59-adjuvanted A/H5N1 influenza vaccine included the A/H5N1/turkey/Turkey/1/2005(-like) antigen (aH5N1).

Treatment

Six different formulations of the aH5N1 vaccine were tested in this dose-finding study: 3 different H5N1 HA antigen dosages (1.875 mg, 3.75 mg, 7.5 mg) and 2 MF59 adjuvant contents (50% and 100%) were evaluated in 5 treatment arms (A-E) together with the licensed dosage for adults (Arm F):

Arm A: 1.875 µg H5N1 antigen + 0.125 mL [50%] MF59 adjuvant;

Arm B: 3.75 µg H5N1 antigen + 0.125 mL [50%] MF59 adjuvant;

Arm C: 7.5 µg H5N1 antigen + 0.125 mL [50%] MF59 adjuvant;

Arm D: 1.875 µg H5N1 antigen + 0.25 mL [100%] MF59 adjuvant;

Arm E: 3.75 µg H5N1 antigen + 0.25 mL [100%] MF59 adjuvant);

Arm F: 7.5 µg H5N1 HA antigen + 0.25 mL [100%] MF59 adjuvant.

The 2-dose vaccine regimen was administrated on Day 1 and Day 22 in an observer-blind manner intramuscularly (anterolateral thigh and deltoid for children aged <2 years and ≥ 2 years, respectively).

Population

Subjects enrolled in the study were healthy male and female subjects of 6 months through <9 years of age. Overall inclusion and exclusion criteria are considered adequate to address the aim of the study and to describe the target population of healthy children/adolescents, more likely not to have pre-existing immunity against influenza viruses. Exclusion of subjects with pandemic influenza illness within past 6 months or ever having received previous pandemic H5N1 flu vaccination or who were administered with other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrolment in this study or who were planning to receive any vaccine prior to Day 43 is acknowledged. Subjects with abnormal function of the immune system due to any cause were excluded; though acceptable, this limits generalizability of study results to immunocompromised paediatric population.

The planned population was randomized with a 1:1:1:1:1:1 ratio among the 6 study arms into two age cohorts: 6-<36 months and 3-<9 years of age, which is considered acceptable and in line with the relevant GL (EMA/CHMP/VWP/457259/2014). Further, the two age cohorts are acknowledged as taking into account possible age effect.

Objectives

The primary immunogenicity objective was to assess the antibody responses to each of the study vaccines at 3 weeks after the first or second vaccination (Day 22 or Day 43), as measured by HI and MN assays.

The secondary immunogenicity objective was to evaluate the persistence of antibody responses to the H5N1 vaccine strain 6 months after the second vaccination (Day 202), as measured by HI and MN assays.

Primary and secondary objectives are adequate to the aim of the study and in line with the guideline (EMA/CHMP/VWP/457259/2014) requirements. Immunogenicity assessment, using HI and MN assays, is comprehensive of the immunological data (Day 1, Day 22, Day 43 GMTs with 95% confidence intervals, Day 22/Day 1 and Day 43/Day 1 GMRs, seroconversion rates, persistence) required by regulatory guidelines.

Timing of blood sampling seems adequate to the 2-dose vaccination scheme, however it is of note that for adjuvanted seasonal vaccines follow-up of persistence of response should be investigated up to 12 months after completion of the initial regimen to investigate the need for annual revaccination. However, in the V87_30 study this period is shorter (the last measurement is set at 6 months), but this is reasonable for a vaccine intended for H5/N1 pandemic response.

Absence of efficacy endpoints is acceptable since it is not expected that clinical efficacy should/can be established at the time of the marketing authorisation.

Sample size and statistics

Sample size was not based on formal power calculations. The minimum expected number of subjects expected to be evaluable for statistical analysis was calculated as at least 30 subjects per vaccine group and age cohort.

The statistical analysis was descriptive therefore no inferential tests were in place. The immunogenicity analyses were performed in the PPS Immunogenicity, which was the primary population of interest for the primary and secondary immunogenicity analyses.

Overall, the study design is considered adequate and compliant with GL EMA/CHMP/VWP/457259/2014) and able to provide data on the chosen dose, schedule and support the selection of the antigen-adjuvant ratio of the aH5N1 adjuvanted vaccine.

Efficacy data and additional analyses

A total of 420 subjects were enrolled in the study with comparable numbers in each age cohort (n=210) and treatment arms (approximately n=70 in each). Demographics show a mean age of 49.3 months (SD: 30.82 months), slightly more male subjects (54.3%), and most population being Asian (76.0%) or White (23.8%). Overall general characteristics were well balanced across treatment arms. Study population is characterized by low prevalence of pre-existing influenza immunity, as almost all subjects (97.1%) did not receive influenza vaccine during the previous 2 years; no information is provided regarding proportion of subjects ever been vaccinated during lifetime.

The PPS Immunogenicity used for the immunogenicity analyses consisted of 407 subjects, as 13 subjects were excluded from the PPS Immunogenicity due to protocol deviations.

Primary Immunogenicity Endpoints

Primary immunogenicity endpoint was assessed by HI and MN assays tested against H5N1 pandemic influenza strain in the total population and by age cohort prior to vaccination (Day 1), at 3 weeks after first vaccination (Day 22) and at 3 weeks after second vaccination (Day 43) and measured by GMT, Day 22/Day 1 and Day 43/Day 1GMRs, as well as seroconversion rate.

GMTs and GMRs for HI Titers (Day 1 to Day 43)

Pre-vaccination (Day 1) HI GMT titers against the homologous H5/N1 pandemic influenza were very low in the overall study population across all 6 treatment arms (range: 5.00-5.24) and similar in both age cohorts.

After first vaccine dose (Day 22), HI GMTs showed only minimal increase and Day 22/Day 1 GMRs that ranged from 1.11 to 1.29. Findings were comparable across vaccine arms and age cohorts (subjects 6 months-<36 months of age: 1.05-1.30; subjects 36 months-<9 years of age: 1.08-1.29).

At 3 weeks after second vaccine dose (Day 43), a robust immune response was observed with increased HI GMTs in all treatment arms and Day 43/Day 1 GMRs ranging from 13.77 to 24.98 and showing higher titers in subjects aged 6 months-<36 months (range, 18.27-31.39) in respect to subjects aged 36 months-<9 years (range, 9.83-23.34). Overall, these finding confirm that the licensed 2-dose regimen, with a second vaccine dose administered 3 weeks after the first, is essential to elicit an adequate antibody response.

Day 43 GMT and Day 43/Day1 GMR increases were consistently higher in D, E, F arms characterized by 100% dose of MF59 content (ranging from 122.43 to 123.61 for GMTs and from 24.35 to 24.98 for GMRs) as compared to A, B, C arms conversely characterized by 50% of MF59 content (ranging from 68.06 to 86.70 for GMTs and from 13.77 to 16.38 for GMRs), suggesting that antibody response is enhanced by the MF59 content (50%<100%). This finding was confirmed across age cohorts.

Regards to antigen dose, no clear effect on immunogenicity is observed, with lower doses achieving similar antibody responses. In vaccine arms D, E, F with 100% MF59 content, HI GMTs at Day 43 (122.43, 123.37, 123.61, respectively) and Day 43/Day 1 GMRs (24.35, 24.98, 23.14, respectively) did not show relevant differences by decreasing antigen dose. Instead results obtained by MN assay seem to show slightly lower immune responses for Arm D (Day 43 GMT 619.44, Day 43/Day 1 GMR 119.78) compared to Arms E (Day 43 GMT 864.91, Day 43/Day 1 GMR 168.06) and F (Day 43 GMT 766.18, Day 43/Day 1 GMR 144.55).

Analysing GMT and GMRs results by age cohorts, as expected younger subjects (6-<36 months) in respect to the older age cohort (3 years -<9 years) seem to show better immunogenicity results,

supporting the advantage of using the MF59-adjuvanted in priming an immune response in immunologically naive subjects, like young children.

Percentage of subjects with HI seroconversion and percentage of subjects with HI titer ≥1:40 (Day 1 to Day 43)

As there were no differences between the percentage of subjects with seroconversion (non-detectable titer at D1 to ≥1:40, or 4-fold increase from a detectable Day 1 titer) and the percentage of subjects with HI titer ≥1:40 at Day 22 or Day 43 in the overall study population or either of the age cohorts, the results for these two study outcomes were overlapping and are presented only once.

In the study population, the percentage of subjects with HI titer >1:40 at baseline (Day 1) was very low across all study arms (range, 0-1.5%) and only minimal increases were observed at Day 22 (range, 0-4,5%). Results were consistent in the two age cohorts. At 3 weeks after second dose (Day 43) percentage of subjects with seroconversion importantly increased reaching 74.6-90.9% of study population. Higher percentages were found in the younger age group (range, 79.4-93.9%) than in the older age group (range, 67.6-87.9%).

In line with what already described for GMTs and GMRs, when analysing data regarding MF59 content, lower seroconversion rates were observed in treatment arms A-C when compared to those recorded for treatment arms D-F, again confirming that 100% adjuvant content is relevant to boost immune response (Overall study population: arms A-C range, 74.6-82.1% *versus* arms D-F range, 86.6-90.9%).

MN test results

Overall, MN assay test results are consistent with those obtained with the HI assay. However, higher antibody titers were observed confirming literature data suggesting the MN functional test (showing neutralizing antibody titres) to be a more sensitive than HI method for detection of antibodies to H5N1 viruses.

Secondary Immunogenicity Endpoints

Secondary immunogenicity endpoints looked at persistence of immunological responses to the different vaccine formulations by comparing response as measured by HI and MN antibody titers on Day 202 (i.e., 6 months after second vaccination). Analysis was carried out in the total population and by age cohort.

At Day 202, HI and MN assays both showed GMTs and GMRs against the H5N1 pandemic influenza homologous strain that are decreased in respect to Day 43 for all vaccination groups. However, Day 202/Day 1 GMRs were increased in respect to baseline and superior in the 100% MF59 vaccine groups (Arms D, E, F) than in the 50% MF59 groups (Arms A, B, C), suggesting that higher adjuvant content is associated with longer persistence of antibody response; this was confirmed when analysing data by age cohorts.

The highest percentages of subjects with an antibody titre >1:40 (or seroconversion) at 6 months after second vaccine dose by both HI and MN assays was found in Arm F (HA antigen-adjuvant ratio 7.5 µg/100% MF59) with, respectively, 25.4% and 98.5% of the study population. While in respect to Arm F, lower HI seroconversion rates were found in Arm D (15.2%), Arm E performed similarly (21.7%) in the overall population. Consistent differences across Arms D-F were reported for the two age cohorts, that however displayed a superior immune response in younger children (Arm D 27.1% versus Arm E 33.3% and Arm F 41.9%) than in older children (Arm D 3.0% versus Arm E 9.1% and Arm F 11.1%).

Although there seems to be no clear difference in HI nor MN response at D202 between arms E (3.75ug/100% MF59) and F (7.5ug/100% MF59), the MAH concludes that the Day 202 immunogenicity results support the use of the formulation containing the higher MF59 content (100% MF59) in

combination with the highest antigen dose (7.5 µg H5N1 HA) that was evaluated in Arm F, which corresponds to the current adult licensed formulation. An important caveat here is that the study included relatively small groups and was not designed to detect any differences between specific groups.

2.4.3. Conclusions on the clinical efficacy

Overall, the results from study V87_30 indicate that Aflunov is immunogenic in children from 6 months to <9 years of age.

While after the first vaccine dose only minimal antibody responses are observed, increased titers are shown at 3 weeks after the second dose for all treatment arms, confirming that the 2-dose vaccine schedule is necessary to elicit immune response.

Overall, subjects belonging to the younger age group (6–<36 months) displayed a higher immune response than older subjects (36 months-<9 years), suggesting that not-primed immune system in children enhances vaccine response.

All immunogenicity data at 3 weeks and 6 months after second vaccine dose support that a 100% MF59 content is needed in the monovalent H5N1 pandemic preparedness vaccine to elicit an increased immunogenicity compared to that achieved with lower adjuvant content. This is confirmed across age cohorts.

With regards to antigen dose, no clear effect on immunogenicity is observed, with lower doses achieving similar antibody responses, particularly in Arm E and F.

The highest percentages of subjects with an antibody titre >1:40 (or seroconversion) at 6 months after second vaccine dose by both HI and MN assays was found in Arm F (HA antigen-adjuvant ratio 7.5 µg/100%) with 25.4% and 98.5%, respectively.

In conclusion, all immunogenicity endpoints confirm that a higher adjuvant content is needed to elicit a greater antibody response across age cohorts. Among vaccine formulations with 100% MF59, the licensed adult dose containing 7.5 µg H5N1 antigen and 0.25 mL MF59, and half adult antigen dose, showed similar antibody responses, while for the smaller antigen formulation a trend towards lower immune responses were reported. Therefore, the proposed dose for the paediatric population, that is the same as for adults (7.5 µg+100% MF59) is considered appropriate. This is also supported by results from study V87_P6 in children 6 months to 17 years of age and by Focetria information that was approved and used with the same antigen-adjuvant adult dose as Aflunov both in adult and paediatric populations. According to SmPC guideline, section 5.1 also mentions immunogenic results from half adult antigen.

2.5. Clinical safety

Introduction

The incidence of adverse reactions has been evaluated in seven clinical trials in healthy subjects involving over 4300 adults and elderly receiving AFLUNOV (at least 7.5 µg HA, adjuvanted). The safety profile across clinical studies using AFLUNOV containing either the A/turkey/Turkey/1/2005 or the A/Vietnam/1194/2004 strain is comparable.

Consistent with the data observed by trial for solicited reactions, there was a general trend towards decreased reports of local reactions after the second vaccination compared with the first injection. Irrespective of antigen dose, almost all systemic reactions were reported on the day of vaccination (day 1) or during the 3 days immediately following. No increase in reactions was reported when a booster dose was administered 6 months-18 months later, after the initial dosing series. A slight increase in reactions in adults was reported when a booster dose was administered 18 months after the initial dosing series. In the elderly, the reported reactions increased with the third booster dose only when compared with the second dose.

The incidence of AFLUNOV (A/Vietnam/1194/2004) adverse reactions has been evaluated in one clinical trial (V87P6) in children (6 months to 17 years old). Regardless of age, reactogenicity was higher after the first dose than after the second vaccination. Reactogenicity after the third dose, administered 12 months following the first dose, was higher than after both first and second doses. The percentages of subjects reporting local reactions were higher in the older age groups, mainly due to the higher reports for pain. In toddlers, erythema and tenderness were the most commonly reported solicited local reactions; irritability and unusual crying were the most commonly reported solicited systemic reactions. In children and adolescents, pain was the most frequently reported solicited local reaction, and fatigue and headache were the most commonly reported solicited systemic reactions. Across all ages, low percentages of subjects reported fever.

Patient exposure

The number of subjects included in each safety analysis set is shown in table below.

No subjects were excluded from the safety sets. All of the 420 subjects in the All Exposed Set had solicited and unsolicited AE data, and were therefore included in the Solicited Safety Set, Unsolicited Safety Set, and Overall Safety Set. In each of the safety sets, there were 210 subjects in both the 6 months to <36 months age cohort and the 3 years to <9 years age cohort.

Table 17: Overview of Safety Sets Analysed – As Treated – All Exposed Set

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) n (%)	Arm B (3.75 µg/50%) n (%)	Arm C (7.5 µg/50%) n (%)	Arm D (1.875 µg/100%) n (%)	Arm E (3.75 µg/100%) n (%)	Arm F (7.5 µg/50%) n (%)	Total n (%)
6 Months to <9 Years	**N=69**	**N=72**	**N=70**	**N=70**	**N=69**	**N=70**	**N=420**
All Exposed Set	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
Solicited Safety Set	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
Unsolicited Safety Set	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
Overall Safety Set	69 (100.0)	72 (100.0)	70 (100.0)	70 (100.0)	69 (100.0)	70 (100.0)	420 (100.0)
6 Months to <36 Months	**N=35**	**N=35**	**N=35**	**N=35**	**N=36**	**N=34**	**N=210**
All Exposed Set	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
Solicited Safety Set	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
Unsolicited Safety Set	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
Overall Safety Set	35 (100.0)	35 (100.0)	35 (100.0)	35 (100.0)	36 (100.0)	34 (100.0)	210 (100.0)
3 Years to <9 Years	**N=34**	**N=37**	**N=35**	**N=35**	**N=33**	**N=36**	**N=210**
All Exposed Set	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
Solicited Safety Set	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
Unsolicited Safety Set	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)
Overall Safety Set	34 (100.0)	37 (100.0)	35 (100.0)	35 (100.0)	33 (100.0)	36 (100.0)	210 (100.0)

Source: Section 5.3.5.1 CSR V87_30.
Abbreviations: AE = adverse event; N = total number of subjects; n = number of subjects with values in category.
Note 1: The All Exposed Set is all subjects in the All Enrolled Set who received at least one dose of study vaccination.
Note 2: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data collected, including temperature measurements or use of analgesics/antipyretics.
Note 3: The Unsolicited Safety Set is all subjects in the All Exposed Set with unsolicited AE data.
Note 4: The Overall Safety Set is all subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.
Note 5: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

The evaluation of the safety profile of Aflunov in paediatric population aged 6 months to <9 years is based upon a dose-ranging paediatric study (V87_30) completed for H5N1, in which 420 subjects were enrolled in the study. A total of 210 subjects were exposed in each of the safety set in both the 6 months to <36 months age cohort and the 3 years to <9 years age cohort and had solicited and unsolicited AE.

Considering that only 70 subjects received the adult dose (7.5 µg/100%), the one finally chosen also for children, the safety database of paediatric study V87_30 is considered small, limiting the detection of rare AEs. However, the safety profile of Aflunov in children is known also from study V87P6, which is of reassurance, even if pooled data would have been more informative in this population. Information on specific longer-term, and rare and very rare AEs, such as the risk of narcolepsy or Guillain-Barré syndrome, should be evaluated post-licensure, also according to Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014).

Adverse events

A summary of the solicited AEs reported in the Solicited Safety Set is presented for the overall study population and by age cohort in table below.

Table 18: Number (%) of Subjects with Solicited Adverse Events From Day 1 Through Day 7 After Vaccination, Overall and by Age Cohort – As Treated – Solicited Safety Set

(H5N1 HA antigen dose/MF59 content)	Arm A (1.875 µg/50%) n (%)	Arm B (3.75 µg/50%) n (%)	Arm C (7.5 µg/50%) n (%)	Arm D (1.875 µg/100%) n (%)	Arm E (3.75 µg/100%) n (%)	Arm F (7.5 µg/100%) n (%)	Total n (%)
6 Months to <9 Years	**N=69**	**N=72**	**N=70**	**N=70**	**N=69**	**N=70**	**N=420**
Any Vaccination							
Any	32 (46.4)	33 (45.8)	32 (45.7)	34 (48.6)	37 (53.6)	31 (44.3)	199 (47.4)
Local	19 (27.5)	16 (22.2)	16 (22.9)	21 (30.0)	19 (27.5)	17 (24.3)	108 (25.7)
Systemic	21 (30.4)	24 (33.3)	20 (28.6)	24 (34.3)	29 (42.0)	18 (25.7)	136 (32.4)
Analgesic/antipyretic use	9 (13.0)	7 (9.7)	6 (8.6)	5 (7.1)	5 (7.2)	9 (12.9)	41 (9.8)
Vaccination 1							
Any	29 (42.0)	26 (36.1)	25 (35.7)	30 (42.9)	27 (39.1)	27 (38.6)	164 (39.0)
Local	15 (21.7)	11 (15.3)	13 (18.6)	18 (25.7)	13 (18.8)	13 (18.6)	83 (19.8)
Systemic	17 (24.6)	20 (27.8)	14 (20.0)	20 (28.6)	17 (24.6)	16 (22.9)	104 (24.8)
Analgesic/antipyretic use	6 (8.7)	4 (5.6)	2 (2.9)	3 (4.3)	2 (2.9)	8 (11.4)	25 (6.0)
Vaccination 2							
Any	17 (24.6)	23 (31.9)	21 (30.0)	22 (31.4)	22 (31.9)	15 (21.4)	120 (28.6)
Local	12 (17.4)	11 (15.3)	11 (15.7)	13 (18.6)	14 (20.3)	12 (17.1)	73 (17.4)
Systemic	11 (15.9)	15 (20.8)	13 (18.6)	14 (20.0)	17 (24.6)	4 (5.7)	74 (17.6)
Analgesic/antipyretic use	3 (4.3)	3 (4.2)	4 (5.7)	2 (2.9)	4 (5.8)	3 (4.3)	19 (4.5)
6 Months to <36 Months	**N=35**	**N=35**	**N=35**	**N=35**	**N=36**	**N=34**	**N=210**
Any Vaccination							
Any	15 (42.9)	20 (57.1)	18 (51.4)	20 (57.1)	21 (58.3)	15 (44.1)	109 (51.9)
Local	7 (20.0)	10 (28.6)	6 (17.1)	11 (31.4)	8 (22.2)	4 (11.8)	46 (21.9)
Systemic	14 (40.0)	15 (42.9)	16 (45.7)	16 (45.7)	18 (50.0)	11 (32.4)	90 (42.9)
Analgesic/antipyretic use	5 (14.3)	4 (11.4)	4 (11.4)	3 (8.6)	3 (8.3)	6 (17.6)	25 (11.9)
Vaccination 1							
Any	13 (37.1)	17 (48.6)	14 (40.0)	16 (45.7)	15 (41.7)	13 (38.2)	88 (41.9)
Local	4 (11.4)	6 (17.1)	5 (14.3)	8 (22.9)	3 (8.3)	3 (8.8)	29 (13.8)
Systemic	11 (31.4)	14 (40.0)	11 (31.4)	13 (37.1)	12 (33.3)	10 (29.4)	71 (33.8)
Analgesic/antipyretic use	2 (5.7)	2 (5.7)	1 (2.9)	1 (2.9)	1 (2.8)	5 (14.7)	12 (5.7)
Vaccination 2							
Any	9 (25.7)	13 (37.1)	10 (28.6)	15 (42.9)	11 (30.6)	6 (17.6)	64 (30.5)
Local	5 (14.3)	6 (17.1)	3 (8.6)	6 (17.1)	7 (19.4)	3 (8.8)	30 (14.3)
Systemic	8 (22.9)	10 (28.6)	9 (25.7)	11 (31.4)	9 (25.0)	2 (5.9)	49 (23.3)
Analgesic/antipyretic use	3 (8.6)	2 (5.7)	3 (8.6)	2 (5.7)	2 (5.6)	2 (5.9)	14 (6.7)
3 Years to <9 Years	**N=34**	**N=37**	**N=35**	**N=35**	**N=33**	**N=36**	**N=210**
Any Vaccination							
Any	17 (50.0)	13 (35.1)	14 (40.0)	14 (40.0)	16 (48.5)	16 (44.4)	90 (42.9)
Local	12 (35.3)	6 (16.2)	10 (28.6)	10 (28.6)	11 (33.3)	13 (36.1)	62 (29.5)
Systemic	7 (20.6)	9 (24.3)	4 (11.4)	8 (22.9)	11 (33.3)	7 (19.4)	46 (21.9)
Analgesic/antipyretic use	4 (11.8)	3 (8.1)	2 (5.7)	2 (5.7)	2 (6.1)	3 (8.3)	16 (7.6)
Vaccination 1							
Any	16 (47.1)	9 (24.3)	11 (31.4)	14 (40.0)	12 (36.4)	14 (38.9)	76 (36.2)
Local	11 (32.4)	5 (13.5)	8 (22.9)	10 (28.6)	10 (30.3)	10 (27.8)	54 (25.7)
Systemic	6 (17.6)	6 (16.2)	3 (8.6)	7 (20.0)	5 (15.2)	6 (16.7)	33 (15.7)
Analgesic/antipyretic use	4 (11.8)	2 (5.4)	1 (2.9)	2 (5.7)	1 (3.0)	3 (8.3)	13 (6.2)
Vaccination 2							
Any	8 (23.5)	10 (27.0)	11 (31.4)	7 (20.0)	11 (33.3)	9 (25.0)	56 (26.7)
Local	7 (20.6)	5 (13.5)	8 (22.9)	7 (20.0)	7 (21.2)	9 (25.0)	43 (20.5)
Systemic	3 (8.8)	5 (13.5)	4 (11.4)	3 (8.6)	8 (24.2)	2 (5.6)	25 (11.9)
Analgesic/antipyretic use	0	1 (2.7)	1 (2.9)	0	2 (6.1)	1 (2.8)	5 (2.4)

Source: Section 5.3.5.1 CSR V87_30.

Abbreviations: AE = adverse event; N = total number of subjects; n = number of subjects with values in category.

Note 1: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data collected, including temperature measurements or use of analgesics/antipyretics.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Solicited local and systemic reactions from day 1 through day 7 in the overall study population appear to be similar among different H5N1 HA antigen doses and increasing MF59. Moreover, it was noted that the number of subjects with solicited AEs tended to be lower in percentage after vaccination 2 compared to vaccination 1 in each study arm (any AE reported from total population decreased from 39% to 28.6%). Some differences were noted between subjects with age cohorts of 6 months to <36 months and 3 years to <9 years. In particular the percentages of subjects developing solicited systemic AEs were reported in higher percentage in subjects in the 6 months to <36 months age cohort (42.9%) compared to those in the 3 years to <9 years age cohort (21.9%), without important differences among different arms.

Solicited local adverse events

Subjects 6 Months to <36 Months of Age

A summary of solicited local AEs occurring within 7 days after vaccination in the Solicited Safety Set is presented for the 6 months to <36 months age cohort in Table 19 below. For subjects 6 months to <36 months of age, solicited local AEs included injection-site erythema, injection-site induration, injection-site ecchymosis, and injection-site tenderness.

Table 19: Number (%) of Subjects 6 Months to <36 Months of Age With Solicited Local Adverse Events from Day 1 Through Day 7 After Vaccination – As Treated – Solicited Safety Set

(H5N1 HA antigen dose/MF59 content) Solicited Local Adverse Event	Arm A (1.875 µg/50%) N=35 n (%)	Arm B (3.75 µg/50%) N=35 n (%)	Arm C (7.5 µg/50%) N=35 n (%)	Arm D (1.875 µg/100%) N=35 n (%)	Arm E (3.75 µg/100%) N=36 n (%)	Arm F (7.5 µg/100%) N=34 n (%)
Any Vaccination						
Erythema						
Any	2 (5.7)	3 (8.6)	3 (8.6)	3 (8.6)	3 (8.3)	2 (5.9)
Severe	0	0	0	0	0	0
Induration						
Any	1 (2.9)	3 (8.6)	1 (2.9)	3 (8.6)	2 (5.6)	2 (5.9)
Severe	0	0	0	0	0	0
Ecchymosis						
Any	0	1 (2.9)	0	0	0	0
Severe	0	0	0	0	0	0
Tenderness						
Any	5 (14.3)	7 (20.0)	5 (14.3)	8 (22.9)	8 (22.2)	4 (11.8)
Severe	2 (5.7)	0	0	1 (2.9)	2 (5.6)	0
Vaccination 1						
Erythema						
Any	1 (2.9)	2 (5.7)	1 (2.9)	1 (2.9)	1 (2.8)	1 (2.9)
Severe	0	0	0	0	0	0
Induration						
Any	0	1 (2.9)	1 (2.9)	1 (2.9)	1 (2.8)	1 (2.9)
Severe	0	0	0	0	0	0

Ecchymosis						
Any	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Tenderness						
Any	3 (8.6)	5 (14.3)	5 (14.3)	6 (17.1)	3 (8.3)	3 (8.8)
Severe	1 (2.9)	0	0	0	1 (2.8)	0
Vaccination 2						
Erythema						
Any	1 (2.9)	3 (8.6)	3 (8.6)	2 (5.7)	3 (8.3)	2 (5.9)
Severe	0	0	0	0	0	0
Induration						
Any	1 (2.9)	3 (8.6)	0	2 (5.7)	2 (5.6)	2 (5.9)
Severe	0	0	0	0	0	0
Ecchymosis						
Any	0	1 (2.9)	0	0	0	0
Severe	0	0	0	0	0	0
Tenderness						
Any	4 (11.4)	3 (8.6)	2 (5.7)	5 (14.3)	7 (19.4)	3 (8.8)
Severe	1 (2.9)	0	0	1 (2.9)	1 (2.8)	0

Source: Section 5.3.5.1 CSR V87_30.

Abbreviations: AE = adverse event; N = total number of subjects; n = number of subjects with values in category.

Note 1: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data collected, including temperature measurements or use of analgesics/antipyretics.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

The rates of solicited local AEs occurring within 7 days after any vaccination were overall similar between the 6 vaccine groups in the 6 months to <36 months age cohort. Tenderness was the most frequently reported solicited local AE, with rates ranging from 11.8% to 22.9% across the 6 vaccine groups, followed by erythema that occurred in 5.7 and 5.9% of subjects in Arm A and F, respectively, and above 8% in the other arms.

Severe events were reported only for tenderness. Five subjects across 3 vaccine groups reported severe tenderness, which did not persist beyond 3 days after vaccination, as reported by the MAH.

Subjects 3 Years to <9 Years of Age

A summary of solicited local AEs occurring within 7 days after vaccination in the Solicited Safety Set is presented for the 3 years to <9 years age cohort in Table below. For subjects 3 years to <9 years of age, solicited local AEs included injection-site erythema, injection-site induration, injection-site ecchymosis, and injection-site pain.

Table 20: Number (%) of Subjects 3 Years to <9 Years of Age With Solicited Local Adverse Events from Day 1 Through Day 7 After Vaccination – As Treated – Solicited Safety Set

(H5N1 HA antigen dose/MF59 content) Solicited Local Adverse Event	Arm A (1.875 µg/50%) N=34 n (%)	Arm B (3.75 µg/50%) N=37 n (%)	Arm C (7.5 µg/50%) N=35 n (%)	Arm D (1.875 µg/100%) N=35 n (%)	Arm E (3.75 µg/100%) N=33 n (%)	Arm F (7.5 µg/100%) N=36 n (%)
Any Vaccination						
Erythema						
Any	2 (5.9)	2 (5.4)	4 (11.4)	2 (5.7)	2 (6.1)	2 (5.6)
Severe	0	0	0	0	0	0
Induration						
Any	2 (5.9)	0	3 (8.6)	2 (5.7)	3 (9.1)	2 (5.6)
Severe	0	0	0	0	0	1 (2.8)
Ecchymosis						
Any	0	0	0	0	1 (3.0)	0
Severe	0	0	0	0	0	0
Pain						
Any	12 (35.3)	5 (13.5)	10 (28.6)	8 (22.9)	9 (27.3)	13 (36.1)
Severe	1 (2.9)	0	1 (2.9)	0	0	1 (2.8)
Vaccination 1						
Erythema						
Any	2 (5.9)	1 (2.7)	2 (5.7)	2 (5.7)	1 (3.0)	1 (2.8)
Severe	0	0	0	0	0	0
Induration						
Any	2 (5.9)	0	2 (5.7)	1 (2.9)	1 (3.0)	1 (2.8)
Severe	0	0	0	0	0	1 (2.8)
Ecchymosis						
Any	0	0	0	0	1 (3.0)	0
Severe	0	0	0	0	0	0
Pain						
Any	11 (32.4)	5 (13.5)	7 (20.0)	8 (22.9)	9 (27.3)	10 (27.8)
Severe	1 (2.9)	0	1 (2.9)	0	0	1 (2.8)
Vaccination 2						
Erythema						
Any	1 (2.9)	2 (5.4)	3 (8.6)	1 (2.9)	2 (6.1)	2 (5.6)
Severe	0	0	0	0	0	0
Induration						
Any	1 (2.9)	0	3 (8.6)	2 (5.7)	2 (6.1)	1 (2.8)
Severe	0	0	0	0	0	0
Ecchymosis						
Any	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Pain						
Any	7 (20.6)	4 (10.8)	8 (22.9)	6 (17.1)	6 (18.2)	9 (25.0)
Severe	0	0	0	0	0	0

In the 3 years to <9 years age cohort, pain was the most frequently reported solicited local AE, with rates ranging from 13.5% to 36.1% across the 6 vaccine groups. The rates of solicited local AEs were similar between the 6 vaccine groups and the majority were mild or moderate in intensity. One subject reported severe induration and 3 subjects across 3 vaccine groups reported severe pain. However, they seem not to be correlated to the higher adjuvant content.

Subjects 6 Months to <36 Months of Age

A summary of solicited systemic AEs occurring within 7 days after vaccination in the Solicited Safety Set is presented for the 6 months to <36 months age cohort in Table 7. For subjects 6 months to <36

months of age, solicited systemic AEs included change in eating habits, vomiting, diarrhoea, irritability, sleepiness, shivering/chills, and fever.

Table 21: Number (%) of Subjects 6 Months to <36 Months of Age With Solicited Systemic Adverse Events from Day 1 Through Day 7 After Vaccination – As Treated – Solicited Safety Set

Table 7 **Number (%) of Subjects 6 Months to <36 Months of Age With Solicited Systemic Adverse Events from Day 1 Through Day 7 After Vaccination – As Treated – Solicited Safety Set**

(H5N1 HA antigen dose/MF59 content) Solicited Systemic Adverse Event	Arm A (1.875 µg/50%) N=35 n (%)	Arm B (3.75 µg/50%) N=35 n (%)	Arm C (7.5 µg/50%) N=35 n (%)	Arm D (1.875 µg/100%) N=35 n (%)	Arm E (3.75 µg/100%) N=36 n (%)	Arm F (7.5 µg/100%) N=34 n (%)
Any Vaccination						
Change in eating habits						
Any	7 (20.0)	8 (22.9)	3 (8.6)	4 (11.4)	6 (16.7)	4 (11.8)
Severe	1 (2.9)	0	0	1 (2.9)	1 (2.8)	0
Vomiting						
Any	1 (2.9)	5 (14.3)	4 (11.4)	4 (11.4)	1 (2.8)	1 (2.9)
Severe	0	0	0	0	0	0
Diarrhoea						
Any	7 (20.0)	10 (28.6)	9 (25.7)	10 (28.6)	4 (11.1)	4 (11.8)
Severe	0	1 (2.9)	0	1 (2.9)	0	0
Irritability						
Any	8 (22.9)	9 (25.7)	4 (11.4)	6 (17.1)	10 (27.8)	4 (11.8)
Severe	1 (2.9)	0	0	1 (2.9)	0	0
Sleepiness						
Any	9 (25.7)	7 (20.0)	5 (14.3)	6 (17.1)	8 (22.2)	3 (8.8)
Severe	0	2 (5.7)	0	0	0	0
Shivering/chills						
Any	1 (2.9)	1 (2.9)	0	1 (2.9)	0	0
Severe	0	0	0	0	0	0
Fever						
Any	5 (14.3)	5 (14.3)	5 (14.3)	5 (14.3)	1 (2.8)	5 (14.7)
Solicited Systemic Adverse Event	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Severe	0	0	0	0	0	0
Vaccination 1						
Change in eating habits						
Any	4 (11.4)	6 (17.1)	1 (2.9)	3 (8.6)	3 (8.3)	4 (11.8)
Severe	0	0	0	1 (2.9)	0	0
Vomiting						
Any	1 (2.9)	4 (11.4)	2 (5.7)	1 (2.9)	0	1 (2.9)
Severe	0	0	0	0	0	0
Diarrhoea						
Any	7 (20.0)	8 (22.9)	6 (17.1)	8 (22.9)	2 (5.6)	4 (11.8)
Severe	0	0	0	1 (2.9)	0	0
Irritability						
Any	5 (14.3)	6 (17.1)	1 (2.9)	5 (14.3)	6 (16.7)	4 (11.8)
Severe	1 (2.9)	0	0	1 (2.9)	0	0
Sleepiness						
Any	7 (20.0)	7 (20.0)	4 (11.4)	3 (8.6)	8 (22.2)	2 (5.9)
Severe	0	2 (5.7)	0	0	0	0
Shivering/chills						
Any	1 (2.9)	1 (2.9)	0	1 (2.9)	0	0
Severe	0	0	0	0	0	0
Fever						
Any	3 (8.6)	3 (8.6)	0	1 (2.9)	0	4 (11.8)
Severe	0	0	0	0	0	0

Vaccination 2						
Change in eating habits						
Any	4 (11.4)	4 (11.4)	2 (5.7)	2 (5.7)	4 (11.1)	0
Severe	1 (2.9)	0	0	0	1 (2.8)	0
Vomiting						
Any	0	1 (2.9)	2 (5.7)	3 (8.6)	1 (2.8)	0
Severe	0	0	0	0	0	0
Diarrhoea						
Any	2 (5.7)	5 (14.3)	3 (8.6)	4 (11.4)	3 (8.3)	0
Severe	0	1 (2.9)	0	0	0	0
Irritability						
Any	6 (17.1)	4 (11.4)	3 (8.6)	4 (11.4)	5 (13.9)	1 (2.9)
Severe	0	0	0	0	0	0
Sleepiness						
Any	4 (11.4)	4 (11.4)	1 (2.9)	3 (8.6)	1 (2.8)	1 (2.9)
Severe	0	0	0	0	0	0
Shivering/chills						
Any	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Fever						
Any	2 (5.7)	2 (5.7)	5 (14.3)	4 (11.4)	1 (2.8)	1 (2.9)
Severe	0	0	0	0	0	0

Source: Section 5.3.5.1 CSR V87_30.

Abbreviations: AE = adverse event; N = total number of subjects; n = number of subjects with values in category.

Note 1: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data collected, including temperature measurements or use of analgesics/antipyretics.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

In the 6 months to <36 months age cohort the most frequently reported solicited systemic AEs after any vaccination were diarrhoea (11.1% to 28.6%), irritability (11.4% to 27.8%), and sleepiness (8.8% to 25.7%), with few severe events reported. There does not appear to be a trend in frequency of AEs with the increase of H5N1 HA antigen dose and/or MF59 content.

Fever (≥38.0°C) was reported after any vaccination in about 14% of subjects in each vaccine group except in the Arm E (3.75 µg/100%) in which occurred in only one subject (2.8%), maybe due to chance. No subjects had severe fever (≥40.0°C). Overall, the frequencies of diarrhoea and sleepiness seem to decrease from vaccination 1 to vaccination 2 in almost all subgroups. No important differences were noted from vaccination 1 to 2 in the other AEs among subgroups.

Subjects 3 Years to <9 Years of Age

A summary of solicited systemic AEs occurring within 7 days after vaccination in the Solicited Safety Set is presented for the 3 years to <9 years age cohort in Table 8. For subjects 3 years to <9 years of age, solicited systemic AEs included loss of appetite, vomiting, diarrhoea, nausea, fatigue, myalgia, arthralgia, headache, malaise, shivering/chills, and fever.

Table 22: Number (%) of Subjects 3 Years to <9 Years of Age With Solicited Systemic Adverse Events from Day 1 Through Day 7 After Vaccination – As Treated – Solicited Safety Set

(H5N1 HA antigen dose/MF59 content) Solicited Systemic Adverse Event	Arm A (1.875 µg/50%) N=34 n (%)	Arm B (3.75 µg/50%) N=37 n (%)	Arm C (7.5 µg/50%) N=35 n (%)	Arm D (1.875 µg/100%) N=35 n (%)	Arm E (3.75 µg/100%) N=33 n (%)	Arm F (7.5 µg/100%) N=36 n (%)
Any Vaccination						
Loss of appetite						
Any	1 (2.9)	3 (8.1)	3 (8.6)	2 (5.7)	2 (6.1)	0
Severe	0	0	0	0	0	0
Vomiting						
Any	2 (5.9)	0	1 (2.9)	2 (5.7)	3 (9.1)	0
Severe	0	0	0	0	1 (3.0)	0
Diarrhoea						
Any	3 (8.8)	2 (5.4)	2 (5.7)	0	2 (6.1)	2 (5.6)
Severe	0	0	0	0	1 (3.0)	0
Nausea						
Any	2 (5.9)	0	2 (5.7)	1 (2.9)	3 (9.1)	3 (8.3)
Severe	0	0	0	0	1 (3.0)	0
Fatigue						
Any	1 (2.9)	2 (5.4)	4 (11.4)	4 (11.4)	6 (18.2)	3 (8.3)
Severe	0	1 (2.7)	0	0	0	0
Myalgia						
Any	2 (5.9)	0	0	1 (2.9)	1 (3.0)	0
Severe	0	0	0	0	0	0
Arthralgia						
Any	2 (5.9)	0	0	0	1 (3.0)	2 (5.6)
Severe	0	0	0	0	0	0
Headache						
Any	3 (8.8)	2 (5.4)	2 (5.7)	3 (8.6)	3 (9.1)	4 (11.1)
Severe	0	0	0	0	0	0
Malaise						
Any	2 (5.9)	0	2 (5.7)	0	0	0
Severe	0	0	0	0	0	0
Shivering/chills						
Any	2 (5.9)	0	1 (2.9)	1 (2.9)	1 (3.0)	0
Severe	0	0	0	0	0	0
Fever						
Any	3 (8.8)	4 (10.8)	2 (5.7)	2 (5.7)	1 (3.0)	1 (2.8)
Severe	0	0	0	0	0	0
Vaccination 1						
Loss of appetite						
Any	1 (2.9)	3 (8.1)	0	2 (5.7)	1 (3.0)	0
Severe	0	0	0	0	0	0
Vomiting						
Any	1 (2.9)	0	1 (2.9)	2 (5.7)	1 (3.0)	0
Severe	0	0	0	0	0	0
Diarrhoea						
Any	2 (5.9)	2 (5.4)	0	0	1 (3.0)	2 (5.6)
Severe	0	0	0	0	0	0
Nausea						

Any	2 (5.9)	0	1 (2.9)	1 (2.9)	1 (3.0)	2 (5.6)
Severe	0	0	0	0	0	0
Fatigue						
Any	1 (2.9)	1 (2.7)	2 (5.7)	3 (8.6)	4 (12.1)	1 (2.8)
Severe	0	1 (2.7)	0	0	0	0
Myalgia						
Any	2 (5.9)	0	0	1 (2.9)	0	0
Severe	0	0	0	0	0	0
Arthralgia						
Any	2 (5.9)	0	0	0	1 (3.0)	2 (5.6)
Severe	0	0	0	0	0	0
Headache						
Any	3 (8.8)	2 (5.4)	1 (2.9)	2 (5.7)	2 (6.1)	3 (8.3)
Severe	0	0	0	0	0	0
Malaise						
Any	2 (5.9)	0	1 (2.9)	0	0	0
Severe	0	0	0	0	0	0
Shivering/chills						
Any	2 (5.9)	0	1 (2.9)	1 (2.9)	0	0
Severe	0	0	0	0	0	0
Fever						
Any	2 (5.9)	2 (5.4)	0	2 (5.7)	1 (3.0)	1 (2.8)
Severe	0	0	0	0	0	0
Vaccination 2						
Loss of appetite						
Any	0	1 (2.7)	3 (8.6)	1 (2.9)	1 (3.0)	0
Severe	0	0	0	0	0	0
Vomiting						
Any	1 (2.9)	0	0	0	3 (9.1)	0
Severe	0	0	0	0	1 (3.0)	0
Diarrhoea						
Any	1 (2.9)	1 (2.7)	2 (5.7)	0	1 (3.0)	0
Severe	0	0	0	0	1 (3.0)	0
Nausea						
Any	0	0	1 (2.9)	0	3 (9.1)	1 (2.8)
Severe	0	0	0	0	1 (3.0)	0
Fatigue						
Any	0	2 (5.4)	4 (11.4)	3 (8.6)	4 (12.1)	2 (5.6)
Severe	0	0	0	0	0	0
Myalgia						
Any	0	0	0	0	1 (3.0)	0
Severe	0	0	0	0	0	0
Arthralgia						
Any	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Headache						
Any	0	0	1 (2.9)	1 (2.9)	3 (9.1)	1 (2.8)

Severe	0	0	0	0	0	0
Malaise						
Any	0	0	1 (2.9)	0	0	0
Severe	0	0	0	0	0	0
Shivering/chills						
Any	0	0	0	1 (2.9)	1 (3.0)	0
Severe	0	0	0	0	0	0
Fever						
Any	1 (2.9)	2 (5.4)	2 (5.7)	0	1 (3.0)	0
Severe	0	0	0	0	0	0

Source: Section 5.3.5.1 CSR V87_30.
Abbreviations: AE = adverse event; N = total number of subjects; n = number of subjects with values in category.
Note 1: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data collected, including temperature measurements or use of analgesics/antipyretics.
Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

In the 3 years to <9 years age cohort the most frequently reported solicited systemic AEs after any vaccination were fatigue (2.9% to 18.2%) and headache (5.4% to 11.1%) with few severe events reported. The AEs seem to be similar between the groups and without apparent higher rates or severity with the increase of the antigen dose or MF59 content.

Fever (≥38.0°C) was reported after any vaccination by 2.8% to 10.8% of subjects in the 6 vaccine groups.

It was noted that some solicited systemic AEs such as diarrhoea and fever are more common in the younger population (6 months to < 36 months) than in subjects 3 years to < 9 years.

Other Indicators of Reactogenicity

Subjects 6 Months to <36 Months of Age

After Any Vaccination

In all 6 vaccine groups in the 6 months to <36 months age cohort, the majority of subjects recorded body temperature <38.0°C within the 7 days after any vaccination. Low numbers of subjects reported body temperature in the range of 38.0°C to 39.9°C. No subjects reported a body temperature of ≥40.0°C. The proportions of subjects using analgesics/antipyretics within 7 days after any vaccination were low, ranging from 2.9% to 11.4% for prevention of pain and/or fever and from 5.6% to 14.7% for treatment of pain and/or fever.

After Vaccination 1

After Vaccination 1, few subjects in the 6 months to <36 months age cohort reported body temperature in the range of 38.0°C to 39.9°C. No subjects reported a body temperature of ≥40.0°C.

The proportions of subjects using analgesics/antipyretics within 7 days after any vaccination ranged from 0% to 5.9% for prevention of pain and/or fever and from 2.9% to 11.8% for treatment of pain and/or fever.

After Vaccination 2

After Vaccination 2, few subjects in the 6 months to <36 months age cohort reported body temperature in the range of 38.0°C to 39.9°C (Table 9). No subjects reported a body temperature of ≥40.0°C.

The proportions of subjects using analgesics/antipyretics within 7 days after any vaccination ranged from 2.9% to 8.6% for prevention of pain and/or fever and from 2.8% to 8.6% for treatment of pain and/or fever.

Table 23: Number (%) of Subjects 6 Months to <36 Months of Age With Other Solicited Adverse Events from Day 1 Through Day 7 After Vaccination – As Treated – Solicited Safety Set

(H5N1 HA antigen dose/MF59 content) Other Solicited Adverse Event	Arm A (1.875 µg/50%) N=35 n (%)	Arm B (3.75 µg/50%) N=35 n (%)	Arm C (7.5 µg/50%) N=35 n (%)	Arm D (1.875 µg/100%) N=35 n (%)	Arm E (3.75 µg/100%) N=36 n (%)	Arm F (7.5 µg/100%) N=34 n (%)
Any Vaccination						
Body temperature (°C)						
38.0 - 38.4	1 (2.9)	2 (5.7)	4 (11.4)	1 (2.9)	0	1 (2.9)
38.5 - 38.9	3 (8.6)	2 (5.7)	0	3 (8.6)	1 (2.8)	4 (11.8)
39.0 - 39.4	1 (2.9)	0	1 (2.9)	0	0	0
39.5 - 39.9	0	1 (2.9)	0	1 (2.9)	0	0
≥40.0	0	0	0	0	0	0
Analgesic/antipyretic use						
Prevention	3 (8.6)	4 (11.4)	3 (8.6)	1 (2.9)	3 (8.3)	2 (5.9)
Treatment	4 (11.4)	4 (11.4)	4 (11.4)	3 (8.6)	2 (5.6)	5 (14.7)
Vaccination 1						
Body temperature (°C)						
38.0 - 38.4	0	1 (2.9)	0	0	0	1 (2.9)
38.5 - 38.9	3 (8.6)	1 (2.9)	0	1 (2.9)	0	3 (8.8)
39.0 - 39.4	0	0	0	0	0	0
39.5 - 39.9	0	1 (2.9)	0	0	0	0
≥40.0	0	0	0	0	0	0
Analgesic/antipyretic use						
Prevention	1 (2.9)	2 (5.7)	0	0	1 (2.8)	2 (5.9)
Treatment	2 (5.7)	2 (5.7)	1 (2.9)	1 (2.9)	1 (2.8)	4 (11.8)
Vaccination 2						
Body temperature (°C)						
38.0 - 38.4	1 (2.9)	1 (2.9)	4 (11.4)	1 (2.9)	0	0
38.5 - 38.9	0	1 (2.9)	0	2 (5.7)	1 (2.8)	1 (2.9)
39.0 - 39.4	1 (2.9)	0	1 (2.9)	0	0	0
39.5 - 39.9	0	0	0	1 (2.9)	0	0
≥40.0	0	0	0	0	0	0
Analgesic/antipyretic use						
Prevention	2 (5.7)	2 (5.7)	3 (8.6)	1 (2.9)	2 (5.6)	1 (2.9)
Treatment	2 (5.7)	2 (5.7)	3 (8.6)	2 (5.7)	1 (2.8)	1 (2.9)

Source: Section 5.3.5.1 CSR V87_30.
Abbreviations: AE = adverse event; N = total number of subjects; n = number of subjects with values in category.
Note 1: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data collected, including temperature measurements or use of analgesics/antipyretics.
Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Subjects 3 Years to <9 Years of Age

After Any Vaccination

In all 6 vaccine groups in the 3 years to <9 years age cohort, the majority of subjects recorded body temperature <38.0°C within the 7 days after any vaccination. Low numbers of subjects reported body temperature in the range of 38.0°C to 39.9°C. No subjects reported a body temperature of ≥40.0°C.

The proportions of subjects using analgesics/antipyretics within 7 days after any vaccination were low, ranging from 3.0% to 8.8% for prevention of pain and/or fever and from 0% to 8.8% for treatment of pain and/or fever.

After Vaccination 1

After Vaccination 1, few subjects in the 3 years to <9 years age cohort reported body temperature in the range of 38.0 °C to 39.9 °C. No subjects reported a body temperature of ≥40.0°C.

The proportions of subjects using analgesics/antipyretics within 7 days after any vaccination ranged from 0% to 8.8% for prevention of pain and/or fever and from 0% to 8.8% for treatment of pain and/or fever.

After Vaccination 2

After Vaccination 2, few subjects in the 3 years to <9 years age cohort reported body temperature in the range of 38.0°C to 39.9°C. No subjects reported a body temperature of ≥40.0°C. The proportions of subjects using analgesics/antipyretics within 7 days after any vaccination ranged from 0% to 3.0% for prevention of pain and/or fever and from 0% to 6.1% for treatment of pain and/or fever.

Table 24: Number (%) of Subjects 3 Years to <9 Years of Age With Other Solicited Adverse Events from Day 1 Through Day 7 After Vaccination – As Treated – Solicited Safety Set

(H5N1 HA antigen dose/MF59 content) Other Solicited Adverse Event	Arm A (1.875 µg/50%) N=34 n (%)	Arm B (3.75 µg/50%) N=37 n (%)	Arm C (7.5 µg/50%) N=35 n (%)	Arm D (1.875 µg/100%) N=35 n (%)	Arm E (3.75 µg/100%) N=33 n (%)	Arm F (7.5 µg/100%) N=36 n (%)
Any Vaccination						
Body temperature (°C)						
38.0 - 38.4	1 (2.9)	2 (5.4)	1 (2.9)	2 (5.7)	0	1 (2.8)
38.5 - 38.9	1 (2.9)	1 (2.7)	1 (2.9)	0	1 (3.0)	0
39.0 - 39.4	0	1 (2.7)	0	0	0	0
39.5 - 39.9	1 (2.9)	0	0	0	0	0
≥40.0	0	0	0	0	0	0
Analgesic/antipyretic use						
Prevention	3 (8.8)	2 (5.4)	2 (5.7)	2 (5.7)	1 (3.0)	3 (8.3)
Treatment	3 (8.8)	3 (8.1)	1 (2.9)	0	2 (6.1)	2 (5.6)
Vaccination 1						
Body temperature (°C)						
38.0 - 38.4	0	1 (2.7)	0	2 (5.7)	1 (3.0)	1 (2.8)
38.5 - 38.9	1 (2.9)	0	0	0	0	0
39.0 - 39.4	0	1 (2.7)	0	0	0	0
39.5 - 39.9	1 (2.9)	0	0	0	0	0
≥40.0	0	0	0	0	0	0
Analgesic/antipyretic use						
Prevention	3 (8.8)	1 (2.7)	1 (2.9)	2 (5.7)	0	3 (8.3)
Treatment	3 (8.8)	2 (5.4)	0	0	1 (3.0)	1 (2.8)
Vaccination 2						
Body temperature (°C)						
38.0 - 38.4	1 (2.9)	1 (2.7)	1 (2.9)	0	0	0
38.5 - 38.9	0	1 (2.7)	1 (2.9)	0	1 (3.0)	0
39.0 - 39.4	0	0	0	0	0	0
39.5 - 39.9	0	0	0	0	0	0
≥40.0	0	0	0	0	0	0
Analgesic/antipyretic use						
Prevention	0	1 (2.7)	1 (2.9)	0	1 (3.0)	1 (2.8)
Treatment	0	1 (2.7)	1 (2.9)	0	2 (6.1)	1 (2.8)

Source: Section 5.3.5.1 CSR V87_30.
Abbreviations: AE = adverse event; N = total number of subjects; n = number of subjects with values in category.
Note 1: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data collected, including temperature measurements or use of analgesics/antipyretics.
Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

The majority of subjects recorded body temperature <38.0°C within the 7 days after any vaccination. Overall, low numbers of subjects reported body temperature in the range of 38.0°C to 39.9°C and no subjects reported a body temperature of ≥40.0°C. However, if considering younger children (6 Months to <36 Months), a slightly higher rate of Other Solicited AEs (Body temperature >38.5-38.9 °C) after any vaccination was noted in Arm F (11.8%) compared to other treatment arms (arm E: 2.8%, D: 8.6%), but only after vaccination 1. Also, the analgesic/antipyretic treatment use seems to be higher in arm F (14.7%) vs arm E (5.6%) and D (8.6%).

Unsolicited Adverse Events

Subjects 6 Months to <9 Years of Age

In the overall study population, the proportion of subjects reporting any unsolicited AE was comparable between the 6 vaccine groups, ranging from 14.3% to 28.6%. Across the 6 vaccine groups, unsolicited AEs were most commonly reported in the SOC of "Infections and infestations". The most commonly reported unsolicited AEs in the overall study population were upper respiratory tract infection (29/420 subjects, 6.9%), gastroenteritis (8/420 subjects, 1.9%), rhinitis (8/420 subjects, 1.9%), and nasopharyngitis (7/420 subjects, 1.7%).

Subjects 6 Months to <36 Months of Age

In the 6 months to <36 months age cohort, the proportion of subjects reporting any unsolicited AEs was comparable between the 6 vaccine groups, ranging from 20.6% to 37.1%.

Unsolicited AEs were most commonly reported in the SOC of "Infections and infestations". Upper respiratory tract infection was the most commonly reported unsolicited AE, reported in 2.9% to 20.0% of subjects across the 6 vaccine groups.

Subjects 3 Years to <9 Years of Age

In the 3 years to <9 years age cohort, the proportion of subjects reporting any unsolicited AE was comparable between the 6 vaccine groups, ranging from 5.7% to 21.2%. Unsolicited AEs were most commonly reported in the SOC of "Infections and infestations". Upper respiratory tract infection was the most commonly reported unsolicited AE, reported in 0% to 9.1% of subjects across the 6 vaccine groups. The rates of related unsolicited AEs were low across the 6 vaccine groups in the 3 years to <9 years age cohort, ranging from 0% to 3.0%. The rates of unsolicited AEs tended to be lower in the 3 years to <9 years age cohort (5.7% to 21.2%) than the vaccine groups in the 6 months to <36 months age cohort (20.6% to 37.1%).

Table 25: Number (%) of Subjects With Related Unsolicited Adverse Events Within 21 Days After Vaccination, Overall and by Age Cohort, by System Organ Class and Preferred Term – As Treated – Unsolicited Safety Set

(H5N1 HA antigen dose/MF59 content) System Organ Class	Arm A (1.875 µg/50%)	Arm B (3.75 µg/50%)	Arm C (7.5 µg/50%)	Arm D (1.875 µg/100%)	Arm E (3.75 µg/100%)	Arm F (7.5 µg/100%)
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
6 Months to <9 Years	**N=69**	**N=72**	**N=70**	**N=70**	**N=69**	**N=70**
Any related unsolicited AE	**2 (2.9)**	**2 (2.8)**	**2 (2.9)**	**0**	**2 (2.9)**	**1 (1.4)**
Gastrointestinal disorders	**0**	**1 (1.4)**	**0**	**0**	**0**	**0**
Diarrhoea	0	1 (1.4)	0	0	0	0
General disorders and administration site conditions	**0**	**1 (1.4)**	**1 (1.4)**	**0**	**1 (1.4)**	**0**
Injection site bruising	0	0	1 (1.4)	0	1 (1.4)	0
Injection site induration	0	1 (1.4)	0	0	0	0
Infections and infestations	**1 (1.4)**	**0**	**0**	**0**	**1 (1.4)**	**1 (1.4)**
Gastroenteritis	0	0	0	0	1 (1.4)	1 (1.4)
Respiratory tract infection	1 (1.4)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**1 (1.4)**	**0**	**0**	**0**	**0**	**0**
Bronchial hyperreactivity	1 (1.4)	0	0	0	0	0
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (1.4)**	**0**	**0**	**0**
Urticaria	0	0	1 (1.4)	0	0	0
6 Months to <36 Months	**N=35**	**N=35**	**N=35**	**N=35**	**N=36**	**N=34**
Any related unsolicited AE	**1 (2.9)**	**2 (5.7)**	**2 (5.7)**	**0**	**1 (2.8)**	**0**
Gastrointestinal disorders	**0**	**1 (2.9)**	**0**	**0**	**0**	**0**
Diarrhoea	0	1 (2.9)	0	0	0	0
General disorders and administration site conditions	**0**	**1 (2.9)**	**1 (2.9)**	**0**	**0**	**0**
Injection site bruising	0	0	1 (2.9)	0	0	0
Injection site induration	0	1 (2.9)	0	0	0	0
Infections and infestations	**0**	**0**	**0**	**0**	**1 (2.8)**	**0**
Gastroenteritis	0	0	0	0	1 (2.8)	0
Respiratory, thoracic and mediastinal disorders	**1 (2.9)**	**0**	**0**	**0**	**0**	**0**
Bronchial hyperreactivity	1 (2.9)	0	0	0	0	0
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (2.9)**	**0**	**0**	**0**
Urticaria	0	0	1 (2.9)	0	0	0
3 Years to <9 Years	**N=34**	**N=37**	**N=35**	**N=35**	**N=33**	**N=36**
Any unsolicited AE	**1 (2.9)**	**0**	**0**	**0**	**1 (3.0)**	**1 (2.8)**
General disorders and administration site conditions	**0**	**0**	**0**	**0**	**1 (3.0)**	**0**
Injection site bruising	0	0	0	0	1 (3.0)	0
Infections and infestations	**1 (2.9)**	**0**	**0**	**0**	**0**	**1 (2.8)**
Gastroenteritis	0	0	0	0	0	1 (2.8)
Respiratory tract infection	1 (2.9)	0	0	0	0	0

Source: Section 5.3.5.1 CSR V87_30.

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subjects with values in category.

Note 1: The Solicited Safety Set is all subjects in the All Exposed Set with any solicited AE data and/or indicators of solicited AEs.

Note 2: As treated: according to the vaccine a subject received, rather than the vaccine to which the subject was randomized.

Note 3: Coded using MedDRA version 25.0.

Note 4: Related AEs include AEs that were considered to be at least possibly related to study vaccination by the Investigator.

The rates of any unsolicited AEs in the overall population (subjects 6 Months to <9 Years of Age) within 21 days after vaccination were similar in the different arms without a particular trend and ranging from 14.3% to 28.6%. The most common AEs by SOC were infections and infestations (from 8.6% to 23.2%) mainly driven by upper respiratory tract infection followed by gastroenteritis. Cough was reported in 2 subjects in the age cohort 6-36 months administered with 3.75 ug/50% Adj. Moreover, a higher rate of any unsolicited AEs was observed in younger children (20.6% to 37.1%) compared to the 3 years to <9

Years of age group (5.7% to 21.2%) which could be of concern. However, if we look at the related unsolicited AEs, even if again more frequent in the younger age group, the range of frequencies decreased and were from 0% to 2.9% in the overall population. There did not appear to be a pattern of related unsolicited AEs associated with the H5N1 HA or MF59 content of the vaccine formulations. Some unsolicited ADRs such as gastroenteritis and bronchial hyperreactivity which occurred in no more than one subject per group, were not included in SmPC section 4.8, since biological implausibility did not allow to conclude on a causal relationship. Urticaria was considered as related AE (frequency Uncommon) since already characterised and previously listed in the post-marketing section of the Aflunov SmPC referred to experience with H1N1v (Focetria licensed for use from 6 months of age during the 2009 influenza pandemic, and containing the same MF59 adjuvant and manufactured with the same process as Aflunov).

Serious adverse event/deaths/other significant events

In the overall study population, 8 of 420 subjects (1.9%) reported 12 SAEs during the study, most commonly in the SOC of "Injury, poisoning and procedural complications", with 4 subjects reporting an SAE of "animal bite". The proportion of subjects reporting SAEs was low across the 6 vaccine groups, ranging from 0% to 4.3%. None of the SAEs were assessed as related to the study vaccine.

In the 6 months to <36 months age cohort, 5 of 210 subjects (2.4%) reported 9 SAEs; in the 3 years to <9 years age cohort, 3 of 210 subjects (1.4%) reported 3 SAEs.

There was 1 unsolicited AE leading to death in the study. The subject (in the 6 months to <36 months age cohort in Arm B) had an SAE of brain neoplasm with a fatal outcome, which was assessed by the Investigator and Sponsor as not related to the study vaccine.

The overall incidence of SAEs was low, with 8 of 420 subjects (1.9%) reporting SAEs, none of which were considered related to the study vaccine.

Deaths

In the overall study population, there was 1 death reported during the study, due to an AE assessed as not related to the study vaccine.

One subject in Arm B (3.75 µg of HA antigen and 0.125 mL [50%] of MF59) (Subject 60803-022), aged 34 months at the time of enrolment in the study, had an SAE of brain neoplasm (onset: Study Day 222) with a fatal outcome (Study Day 377). This subject also experienced SAEs of Klebsiella pneumoniae bacteraemia (2 events: onset/resolution of first event: Study Day 234/Study Day 254; onset/resolution of second event: Study Day 259/Study Day 271) and septic shock (onset/resolution: Study Day 259/Study Day 262). The Investigator and Sponsor assessed the 4 SAEs as not related to the study vaccine.

Two cases of febrile convulsion were reported in two children aged 6 months to < 36 months as SAEs in the two formulations with higher antigen H5N1 HA ad MF59 content. These events were assessed as not related to the study vaccine due to implausible temporal relationship and/or alternative cause. However, cases of convulsions with and without fever have been reported in subjects vaccinated with Focetria, an MF59.1 adjuvanted H1N1 pandemic vaccine similar to Aflunov, therefore, this information is included in 4.4 section of the SmPC. It is also noted in the SmPC that the majority of febrile convulsions occurred in paediatric subjects and were observed in subjects with a history of epilepsy.

Laboratory findings

No safety-related clinical laboratory data were collected in Study V87_30.

Vital Signs, Physical Findings, and Other Observations Related to Safety

All clinically relevant changes in physical findings or vital signs such as heart rate and blood pressure were to have been reported as unsolicited AEs during the study and were not collected separately.

Safety in special populations

Intrinsic Factors

Safety analyses stratified by age (3 months to <36 months versus 3 years to <9 years of age) are presented in the previous sections. No other analyses of intrinsic factors were undertaken.

Extrinsic Factors

No analyses of extrinsic factors were undertaken.

Safety related to drug-drug interactions and other interactions

Co-administration of vaccines was not investigated in the study. A list of concomitant medications, by subject and treatment group, is provided in efficacy section.

Discontinuation due to adverse events

No AE resulted in withdrawal from the study.

Post marketing experience

No post-marketing data are available for aH5N1 vaccine

2.5.1. Discussion on clinical safety

All 420 subjects enrolled in study V87_30 were included in the Solicited Safety Set, Unsolicited Safety Set, and Overall Safety Set, in each of which there were 210 subjects in both the 6 months to <36 months age cohort and the 3 years to <9 years age cohort.

Considering that only 70 subjects received the adult dose (7.5 µg/100%), the one proposed by the MAH also for children, the safety database of paediatric study V87_30 is considered small, limiting the detection of the rare AEs. However, the safety profile of Aflunov in children is known also from study V87P6, which is of reassurance, even if pooled data would have been more informative in this population. Information on specific longer-term, and rare and very rare adverse events, such as the risk of narcolepsy or Guillain-Barré syndrome, should be evaluated post-licensure, also according to Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014).

Overall, solicited local and systemic reactions from day 1 through day 7, in the 6 months to <9 years study population appear to be similar among different H5N1 HA antigen doses and increasing MF59 content. It was noted that the number of subjects with solicited AEs tended to be lower in percentage after vaccination 2 compared to vaccination 1 in each study arm (any AE reported from total population decreased from 39% to 28.6%).

Some differences were noted between subjects with age cohorts of 6 months to <36 months and 3 years to <9 years. In particular, the percentages of subjects developing solicited systemic AEs were reported in higher percentage in subjects in the 6 months to <36 months age cohort (42.9%) compared to those in the 3 years to <9 years age cohort (21.9%) without important differences among different arms.

Adverse Drug Reactions (ADRs) were re-arranged in a single table in SmPC section 4.8 relevant for adults, elderly and paediatric subjects, including solicited and unsolicited related AEs.

Solicited local AEs

The rates of solicited local AEs occurring within 7 days after any vaccination were overall similar between the 6 vaccine groups in the 6 months to <36 months age cohort with injection-site tenderness being the most frequently reported solicited local AE (rates ranging from 11.8% to 22.9% across the 6 vaccine groups) followed by injection-site erythema that occurred in 5,7 and 5.9% of subjects in Arm A and F, respectively, and above 8% in the other arms. Few severe events were reported only for tenderness (five subjects across 3 vaccine groups), which did not persist beyond 3 days after vaccination, as reported by the MAH.

In the 3 years to <9 years age cohort, injection-site pain was the most frequently reported solicited local AE, with rates ranging from 13.5% to 36.1% across the 6 vaccine groups. The rates of solicited local AEs were similar between the 6 vaccine groups and the majority were mild or moderate in intensity. One subject reported severe injection-site induration and 3 subjects across 3 vaccine groups reported severe injection-site pain. However, they seem not to be correlated to the higher antigen dose nor adjuvant content.

Solicited systemic AEs

In the 6 months to <36 months age cohort the most frequently reported solicited systemic AEs after any vaccination were diarrhoea (11.1% to 28.6%), irritability (11.4% to 27.8%), and sleepiness (8.8% to 25.7%), with few severe events reported. There does not appear to be a trend in frequency of AEs with the increase of H5N1 HA antigen dose and/or MF59 content. Fever (⩾38.0° C) was reported after any vaccination in about 14% of subjects in each vaccine group except in the Arm E (3.75 µg/100%) in which occurred in only one subject (2.8%), maybe due to chance. No subjects had severe fever (⩾40.0°C). Overall, the frequencies of diarrhoea and sleepiness seem to decrease from vaccination 1 to vaccination 2 in almost all subgroups. No important differences were noted from vaccination 1 to 2 in the other AEs among subgroups.

In the 3 years to <9 years age cohort the most frequently reported solicited systemic AEs after any vaccination were fatigue (2.9% to 18.2%) and headache (5.4% to 11.1%) with few severe events reported. The AEs seem to be similar between the groups and without apparent higher rates or severity with the increase of the antigen dose or MF59 content. Fever (⩾38.0°C) was reported after any vaccination by 2.8% to 10.8% of subjects in the 6 vaccine groups.

It was noted that some solicited systemic AEs such as diarrhoea and fever are more common in the younger population (6 months to < 36 months) than in subjects 3 years to < 9 years.

The majority of subjects recorded body temperature <38.0° C within the 7 days after any vaccination with low numbers of subjects reported body temperature in the range of 38.0°C to 39.9°C and no subjects reported a body temperature of ⩾40.0°C. A slightly higher rate of Other Solicited AEs (Body temperature >38 °C) was noted in younger children (6 Months to <36 Months) in Arm F compared to other treatment arms, in particular after vaccination 1, together with a greater analgesic/antipyretic use.

Unsolicited AEs

The rates of any unsolicited AEs in the overall population within 21 days after vaccination were similar in the different arm without a particular trend and ranging from 14.3% to 28.6%. A higher rate of any unsolicited AEs was observed in younger children (20.6% to 37.1%) compared to the 3 years to <9 Years

of age group (5.7% to 21.2%) which could be of concern. However, if we look at the related unsolicited AEs, the range of frequencies, even if again slightly higher in the younger age group, decreased and become from 0% to 2.9% (in the overall population).

Among the unsolicited AEs gastroenteritis, bronchial hyperreactivity, upper respiratory tract infection and cough were not considered related to aH5N1 vaccination due to no biological plausibility, although temporal association was observed.

Cough is retained in the post-marketing experience section of Aflunov SmPC (section 4.8), regarding Focetria (H1N1) vaccine, while urticaria was moved from Focetria post-marketing section of Aflunov SmPC ADRs table in section 4.8, since considered related to aH5N1 vaccination, according to data from pediatric study V87_30.

A low number of SAEs were reported in the overall safety population. 1.9% of subjects reported 12 SAEs during the study, most commonly in the SOC of "Injury, poisoning and procedural complications", with 4 subjects reporting an SAE of "animal bite". All SAEs were assessed as unrelated to the study vaccine by the investigator. One death in Arm B (3.75 µg of HA antigen and 0.125 mL [50%] of MF59) occurred due to brain neoplasm, not related to the study vaccine.

Two cases of febrile convulsions occurred in two children aged 6 months to < 36 months and reported as SAEs, no other cases of seizures have been reported in this trial. However, these events of febrile convulsions were judged as not related to the study vaccine due to implausible temporal relationship and/or alternative cause.

Cases of convulsion with and without fever have been reported in subjects vaccinated with Focetria, an MF59.1 adjuvanted H1N1 pandemic vaccine similar to Aflunov, and this information is included in 4.4 section of the SmPC. It is also noted in the SmPC that the majority of febrile convulsions occurred in paediatric subjects and were observed in subjects with a history of epilepsy.

In total, 1 subject in Arm B reported an AE leading to NOCD (asthma) during the study. No subjects reported AESIs or AEs leading to vaccine and/or study withdrawal.

2.5.2. Conclusions on clinical safety

The safety profile of Aflunov in the paediatric population from Study V87_30 is similar to that known from Study V87P6. Overall, solicited local and systemic reactions from day 1 through day 7 appear to be similar among different H5N1 HA antigen doses and increasing MF59 content. However, it may be that the sample size was too small and the population too variable to detect any dose effect. The number of subjects with solicited AEs tended to be lower after vaccination 2 than after vaccination 1 in each study arm. Moreover, solicited systemic AEs seem to occur more frequently in younger children (aged 6 months to < 36 months) compared to those in the 3 years to <9 years age cohort.

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

The PRAC considered that the risk management plan version 5.4 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.4.

The MAH submitted an updated RMP with proposed amendments mainly reflecting inclusion of indication and posology for children 6 months of age and above in the product overview for Aflunov based on the results of the V87_30 clinical study in the paediatric population. It is to note that the version 5.2 of the RMP, not provided during the zoonotic strain change variation as per request by the Agency, was relevant to the influenza virus strain change for Zoonotic Influenza Vaccine Seqirus from H5N1 to H5N8 and to the inclusion of EPSS as routine pharmacovigilance activity for Zoonotic Influenza Vaccine Seqirus and was included among the submitted document by the MAH.

Safety concerns

Table SVIII.1: Summary of the Safety Concerns for aH5N1/aH5N8

Important identified risk	None
Important potential risk	Neuritis Convulsions Encephalitis (*encephalomyelitis*) Vasculitis Guillain-Barré Syndrome Demyelination Bell's palsy Immune thrombocytopenia
Missing information	Use in pregnancy and lactation

Considering the data in the safety specification, the safety concerns listed above are appropriate (no amendments proposed with respect to previous RMP version)

Post-authorisation experience

A reference to the recent dominance of clade 2.3.4.4b lineage of H5 viruses, that required a strain change from H5N1 to the H5N8 A/Astrakhan/3212/2020 (clade 2.3.4.4b) in order for Zoonotic Influenza Vaccine Seqirus to be able to match with the circulating H5 virus has been added to the section.

Identified and potential risks

No modifications with respect to the previous version 5.1 of the RMP, approved within the procedure EMEA/H/C/001208/II/0081

Missing information

The SVII.2 New safety concerns and reclassification with a submission of an updated RMP has been updated by deleting the rationale for removal of the missing information "use in children (6 months to less than 18 years of age)" since it was approved within the procedure EMEA/H/C/001208/II/0081.

Pharmacovigilance plan

ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities for Seqirus products comply with Good Pharmacovigilance Practice (GVP) and fulfil the legal requirements per Directive 2001/83/EC and Regulation (EC) No. 726/2004. Routine pharmacovigilance includes management of Individual Case Safety Reports (ICSRs), Periodic Safety Update Reports (PSURs), monitoring safety profiles, and safety signal detection and evaluation.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific targeted follow-up questionnaires related to pregnancy reporting and outcome; and to important potential risks of Neuritis, Convulsions, Encephalitis (encephalomyelitis), Vasculitis, GBS, Demyelination, Bell's palsy, Immune thrombocytopenia (Annex 4), applicable to Aflunov, Foclivia and Zoonotic Influenza Vaccine Seqirus.

- Enhanced Passive Safety Surveillance (EPSS) for Aflunov (aH5N1) and Zoonotic Influenza Vaccine Seqirus (aH5N8) to be conducted, in collaboration with the respective Public Health Agency, upon the first initiation of a government-directed vaccination programme (in the context of outbreaks of zoonotic influenza viruses with pandemic potential, including use in First Responders, i.e. functions critical to maintain civil infrastructure, when there is anticipation of a possible pandemic due to the same or a similar strain) amongst the purchasing EU countries (or UK)

- Outside of the pandemic period, the normal PSUR periodicity and format will be maintained. In the situation of a pandemic, resources will be concentrated on a timely and effective monitoring of the safety profile of Foclivia (pandemic vaccine) and zoonotic aH5N1/aH5N8 influenza vaccines (if used during pandemic). The normal PSUR will be replaced with simplified PSURs (S-PSURs), accompanied by a summary of vaccine distribution. S-PSURs will be prepared monthly, with clock start the first Monday after shipment of the first batch of vaccine once a pandemic is declared. First DLP is 30 days later, with submission on Day 45. The periodicity will be reviewed in collaboration with competent authorities at 6 monthly intervals.

- In the situation of a pandemic, a business continuity planning and crisis management procedure is also in place which specifically details plans to ensure resource is prioritised and necessary technical requirements are met.

ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

It is considered that for the majority of safety concerns, routine pharmacovigilance activities alone will be sufficient. However, in the situation of a pandemic, required Category 3 Study V87_27OB is planned for Foclivia to address the missing information Use in pregnancy and lactation:

- V87_27OB is a postmarketing, observational cohort study to evaluate the safety of adjuvanted pandemic influenza vaccine A/H5N1* (Foclivia) in pregnant women (pregnancy registry). This study is planned in case of pandemic and will follow from enrolment to pregnancy outcome and in live-born infants until 3 months of age.

* The strain is subject to change to be matched with the next pandemic strain

As a specific post-authorisation pharmacovigilance requirement, in accordance with EMA/CHMP/VWP/457259/2014 Guidance on Influenza Vaccines, the enhanced safety surveillance (ESS) for A/H5N1 (Foclivia) will be performed during the pandemic period aiming to rapidly collect the data within a

month from the start of vaccination. This is a Category 2 study, imposed by the competent authority as a Specific Obligation in the context of marketing authorisation under exceptional circumstances.

An updated RMP with further details on additional pharmacovigilance activities will be submitted to competent authorities once a pandemic is declared.

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Enhanced surveillance of vaccine safety (Foclivia®) (Planned)	To evaluate safety and reactogenicity of Foclivia in the different age groups in terms of local and systemic adverse reactions and any adverse events (AEs) defined as important potential risks.	Neuritis, Convulsions, Encephalitis (encephalomyelitis), Vasculitis, Guillain-Barré Syndrome, Demyelination, Bell's palsy, Immune Thrombocytopenia	EPSS plan (full description outlining implementation) to be provided once pandemic is declared. Milestones to be confirmed.	To be confirmed
Category 3 - Required additional pharmacovigilance activities				
V87_27OB is a postmarketing observational cohort safety study of pandemic influenza A/H5N1* vaccine (Foclivia®) in pregnant women (Planned)	To evaluate the safety of pandemic influenza vaccine in pregnant women.	Use in pregnancy and lactation	Protocol to be provided once pandemic is declared. Milestones to be confirmed.	To be confirmed

** The strain is subject to change to be matched with the next pandemic strain*

Seqirus commits to discuss the results of EPSS for Aflunov and Zoonotic Influenza Vaccine Seqirus in the PSURs and to reflect any changes to the requirement and to the EPSS plan, as applicable, according to the indications of the regulatory authorities, pending the revision of the EMA/PRAC/222346/2014 guideline. A short syntax of the planned activities, once defined according to the revised guideline, will be added in Part III.1.

Overall conclusions on the PhV Plan

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

The studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

2.7. Plans For Post-Authorisation Efficacy Studies

This Part of RMP reports the planned non-interventional study of vaccine effectiveness for Foclivia, to be conducted in the case of a pandemic, in accordance with the Guideline on Influenza vaccine (EMA/CHMP/VWP/457259/2014).

Table Part IV. 1: Planned post-authorisation efficacy studies

Study (Status)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
A non-interventional study of vaccine effectiveness for Foclivia® (Planned)	To perform an analysis of vaccine effectiveness for Foclivia® versus no vaccination	Not applicable	Protocol to be provided when pandemic is declared. Milestones to be confirmed	To be confirmed

Of note, the planned post-authorisation efficacy study has been imposed by the competent authority as a Specific Obligations in the context of marketing authorisation under exceptional circumstances.

Risk minimisation measures

Routine Risk minimization measures.

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Neuritis	Neuritis is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus Summary of Product Characteristics (SmPC) and Section 4 of the Package Leaflet (PL).
Convulsions	Convulsions are described in Section 4.4 Special warning and precautions for use of the Foclivia SmPC and Section 4.8 Undesirable effects of Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 2 & 4 of the PL.
Encephalitis (*encephalomyelitis*)	Neurological disorders, such as encephalomyelitis, are described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 4 of the PL.
Vasculitis	Vasculitis is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 4 of the PL.
Guillain-Barré syndrome	Guillain-Barré syndrome is described in Section 4.8 Undesirable effects of the Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC and Section 4 of the PL.
Demyelination	None; included as a potential safety concern based on pharmacological class effects
Bell's palsy	None; included as a potential safety concern based on pharmacological class effects
Immune thrombocytopenia	None; included as a potential safety concern based on pharmacological class effects

Safety concern	Routine risk minimisation activities
Use in pregnancy and lactation	Use in pregnancy and use during breast-feeding is described in Section 4.6 of Foclivia, Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC; and Section 2 of the PL.

ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of aH5N1/aH5N8.

SUMMARY OF RISK MINIMISATION MEASURES

Table Part V. 2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measure	Pharmacovigilance Activity
Important Identified Risk		
None		
Important Potential Risk		
Neuritis	Routine risk minimisation measures: Neuritis is described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Neuritis targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Convulsions	Routine risk minimisation measures: Convulsions are described in: *Foclivia SmPC: Section 4.4 and 4.8* *Aflunov and Zoonotic Influenza Vaccine Seqirus SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and, Foclivia PL: Section 2 and 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Convulsions targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Encephalitis (*encephalomyelitis*)	Routine risk minimisation measures: Neurological disorders, such as Encephalomyelitis, are described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 4* Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Encephalitis (encephalomyelitis) targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)*

	No additional measures	Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Vasculitis	Routine risk minimisation measures: Vasculitis is described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Vasculitis targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Guillain-Barré syndrome	Routine risk minimisation measures: Guillain-Barré syndrome is described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.8* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 4* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Guillain-Barré syndrome targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Demyelination	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Demyelination targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Bell's palsy	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Bell's Palsy targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)*

		Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Immune thrombocytopenia	Routine risk minimisation measures: None; included as a potential safety concern based on pharmacological class effects Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Immune thrombocytopenia targeted follow-up questionnaire* *EPSS (Aflunov and Zoonotic Influenza Vaccine Seqirus)* Additional pharmacovigilance activities: *Category 2 study - Enhanced surveillance of vaccine safety (Foclivia)*
Missing information		
Use in pregnancy and lactation	Routine risk minimisation measures: Pregnancy and breast-feeding is described in: *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia SmPC: Section 4.6* *Aflunov, Zoonotic Influenza Vaccine Seqirus and Foclivia PL: Section 2* Additional risk minimisation measures: *No additional measures*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: *S-PSUR (in situation of pandemic)* *Pregnancy Reporting/Outcome form (Aflunov, Zoonotic Influenza Vaccine Seqirus, Foclivia)* Additional pharmacovigilance activities: *Category 3 study - V87_27OB (Foclivia)*

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Elements for a public summary of the RMP

The summary of important risks of all 3 vaccines have been revised to list all routine and additional risk minimisation measures.

The elements for a public summary of the RMP do not require further revision before the conclusion of the procedure.

Annexes

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS: the intended use of the forms for each vaccine has been specified.

ANNEX 2 and 3 have been also amended to detail the safety concerns addressed by the studies and their categories.

2.8. Update of the Product information

As a consequence of this new indication sections 4.1, 4.2, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet (PL) has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the product information including updating the

SmPC in line with EMA guidance regarding sodium and potassium content.

Section 4.1 of the SmPC

4.1 Therapeutic indications

Active immunisation against H5N1 subtype of Influenza A virus in individuals 6 months of age and above.

~~This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of the vaccine containing A/turkey/Turkey/1/2005 (H5N1) like strain (see sections 4.4 and 5.1).~~

AFLUNOV should be used in accordance with official recommendations.

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

2.8.1. User consultation

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

As part of this Type II variation, the Aflunov SmPC has been updated to include the results of Study V87_30. In addition, changes have been implemented in the SmPC to increase alignment with text agreed during a Type II variation to include V87_30 for Foclivia (EMEA/H/C/001208/II/0081). The Foclivia Package Leaflet (PL) has been updated in accordance with the changes in the SmPC and to increase alignment with the QRD template. The primary changes in the PL consist of the addition non-serious solicited adverse reaction terms from the paediatric studies (V87P6 and V87_30) and a minor rearrangement of information in section 4, Possible side effects, to present the side effects in decreasing order of seriousness.

Seqirus considers that since none of the changes impact how the product is used and the new studies did not change the safety profile of the product, the additional detail provided in the PL on adverse reactions reported in the paediatric studies are not significant from a safety point of view and thus do not warrant conducting consultation with target patient groups (user testing).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Zoonotic influenza (a zoonosis) occurs when humans are infected with influenza viruses circulating in animals. Human infections are primarily acquired through direct contact with infected animals or contaminated environments.

Aflunov was developed to protect against a zoonotic influenza viral strain closely matched to strains circulating in avian populations at the time of submission, via early vaccination during pre-pandemic stages

(e.g. to reduce mortality in exposed subjects in those countries where infections are occurring). Zoonotic influenza vaccines are intended for active immunisation in the context of an outbreak of zoonotic influenza viruses with pandemic potential, including use in specific groups at high risk of infection from both avian and human viruses like veterinarians or laboratory personnel, and when there is anticipation of a possible pandemic due to the same or similar influenza strain.

Moreover, the zoonotic vaccine may also help reducing the chance of the emergence of a reassortant pandemic strain.

Examples of zoonotic influenza include avian influenza, also known as "bird flu", with virus subtypes A(H5N1) and A(H9N2), and swine influenza, also known as "swine flu", with virus subtypes A(H1N1) and A(H3N2).

Avian influenza viruses have several subtypes, but highly pathogenic avian influenza (HPAI) H5N1, have been associated with hundreds of identified human cases since 1997. Between 2003 and July 18, 2018, 860 laboratory-confirmed human cases of H5N1 virus infection were officially reported to the World Health Organization (WHO) from 16 countries in Asia, Africa, Europe, America and the Near East, with an overall case fatality rate (CFR) of 53% [WHO, 2018].

Almost all of these cases have been epidemiologically linked to close contact with poultry, and while human-to-human transmission has been sporadic, H5N1 HPAI viruses represent a pandemic threat.

3.1.2. Available therapies and unmet medical need

In the event of a zoonotic influenza, vaccines are the most effective means of preventing and controlling the spread of virus amongst the human population.

There is no universal vaccine against zoonotic influenza. The major challenge to developing broadly effective vaccines against zoonotic influenza is that within subtypes there are hundreds of strains that may vary slightly, and which naturally and frequently mutate to create new strains.

Aflunov is a specific vaccine against the particular subtypes influenza A(H5N1). Besides Aflunov, there are currently two other zoonotic influenza vaccines authorised in EU, both from the same marketing authorisation holder (MAH) Seqirus S.r.l.:

-the egg-based "Zoonotic Influenza Vaccine Seqirus" (surface antigen, inactivated, MF59C.1-adjuvanted) based on A/Astrakhan/3212/2020 (H5N8)-like strain (CBER-RG8A) (clade 2.3.4.4b), approved in October 2023 on informed consent by Aflunov, which underwent the strain update from H5N1 to H5N8 in May 2024 (EMEA/H/C/006375/II/0001);

-the cell-based vaccine Celldemic (surface antigen, inactivated, MF59C.1-adjuvanted) based on A/turkey/Turkey/1/2005 (H5N1)-like strain (NIBRG-23), approved in April 2024.

3.1.3. Main clinical studies

The clinical trial supporting dosing regimens in children aged 6 months to <9 years was Study V87_30, a phase 2, randomized, observer-blind, multicenter study aimed at evaluating the immunogenicity and safety of several doses of antigen and MF59 adjuvant content in a monovalent H5N1 pandemic influenza vaccine in healthy paediatric subjects 6 months to <9 years of age.

Eligible subjects were stratified by age at the time of enrolment into one of two age cohorts: 6 months to <36 months of age and 3 years to <9 years of age and randomly assigned (1:1:1:1:1:1) to 1 of 6 vaccine groups.

Subjects in each vaccine group were scheduled to receive 2 injections of the assigned aH5N1 vaccine formulation 3 weeks apart.

In this study, the 5 vaccine formulations with decreased content of HA antigen and/or MF59 adjuvant (Arms A to E) were evaluated together with the formulation containing the licensed dosage for adults of 7.5 µg H5N1 HA antigen in combination with 0.25 mL (100%) MF59 (Arm F).

Immunogenicity data in children 6 months to 17 years of age were also available from study V87_P6 in which Aflunov was administered with the same antigen-adjuvant adult dose.

3.2. Favourable effects

In respect to pre-vaccination status, immune responses by HI and MN assay at 3 weeks after second vaccine dose (Day 43) show for all treatment arms and age cohorts increased GMTs, Day 43/Day 1 GMRs from 13.77 to 24.98, and seroconversion rates between 74.6-90.9%.

As after the first vaccine dose only minimal antibody responses are observed, Day 43 findings confirm that the licensed 2-dose regimen, with a second vaccine dose administered 3 weeks after the first, is essential to elicit antibody response.

All immunogenicity data at three weeks after second vaccine dose as well as persistence of antibody response at 6 months support that a 100% MF59 content is needed in the monovalent H5N1 pandemic preparedness vaccine to elicit a greater immunogenicity compared to that achieved with lower adjuvant content. This is confirmed across age cohorts and regardless of H5N1 HA antigen dose.

The percentages of subjects with HI and MN titre >1:40 at 6 months after second vaccine dose by both HI and MN assays in Arm F (HA antigen-adjuvant ratio 7.5 µg/100%) was 25.4% and 98.5%, respectively.

3.3. Uncertainties and limitations about favourable effects

No efficacy or effectiveness data are available for Aflunov. Presently, as expected for pandemic preparedness vaccines, the 2-dose vaccine regimen is evaluated based on immunogenicity data.

As immunocompromised children were excluded from studies, generalizability of results to this population is not possible.

Little is known on persistence of antibody response and no data are provided on booster dose in children.

Although immunological assessment of influenza vaccines is commonly carried out by HI and MN assays, high intra- and inter-laboratory variability and between-assays agreement are still under scrutiny. Moreover, compared to HI assay, MN has been shown to detect higher proportion of positive samples, and thus to be more sensitive.

For adults and especially children, immune correlates of protection for pandemic influenza strains have not been identified.

Study results provided for antigen-adjuvant ratio dose selection are merely descriptive. Regarding antigen dose, no clear effect on immunogenicity is observed, with half adult dose achieving similar antibody responses to adult dose.

3.4. Unfavourable effects

6 months to <36 months age cohort

The most frequently reported solicited local AEs occurring within 7 days after any vaccination the 6 months to <36 months age cohort were tenderness (rates ranging from 11.8% to 22.9% across the 6 vaccine groups) followed by erythema that occurred in 5.9% of subjects in Arm A and above 8% in the other arms.

In the 6 months to <36 months age cohort the most frequently reported solicited systemic AEs after any vaccination were diarrhoea (11.1% to 28.6%), irritability (11.4% to 27.8%), and sleepiness (8.8% to 25.7%), with few severe events reported. No subjects had severe fever (≥40.0 °C).

3 years to <9 years age cohort

In the 3 years to <9 years age cohort, pain was the most frequently reported solicited local AE, with rates ranging from 13.5% to 36.1% across the 6 vaccine groups.

In the 3 years to <9 years age cohort the most frequently reported solicited systemic AEs after any vaccination were fatigue (2.9% to 18.2%) and headache (5.4% to 11.1%) with few severe events reported. Fever (≥38.0°C) was reported after any vaccination by 2.8% to 10.8% of subjects in the 6 vaccine groups.

A slightly higher rate of Other Solicited AEs (Body temperature >38 °C) was noted in younger children (6 Months to <36 Months) in Arm F compared to other treatment arms after vaccination 1 only, together with a greater analgesic/antipyretic use.

3.5. Uncertainties and limitations about unfavourable effects

The safety database is limited. A total of 420 subjects aged 6 months to <9 years received Aflunov in paediatric study V87_30 and only 70 subjects, equally divided among each age cohort, received the adult dose (7.5 µg/100%), the one chosen by the MAH also for children, limiting the detection of the rarer AEs as well as any different dose effect. However, the safety profile of Aflunov in children population in terms of antigen and adjuvant contents is known also from study V87_P6 and from data on Focetria, which is of some reassurance.

3.6. Effects Table

Table 1. Effects Table for Aflunov

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Antibody response	HI GMR Day 43/Day 1 (95% CI)	Ratio	For Arms A-C: 13.77-16.38 For Arms D-F: 23.14-24.98	N/A	Immunogenicity data support that a 100% MF59 content is needed to elicit a greater immunogenicity compared to that achieved with lower adjuvant content.	
SCR	Percentage of subjects with HI seroconversion at Day 43 (95% CI)	%	For Arms A-C: 74.6-82.1% For Arms D-F: 86.6-90.9%			
Unfavourable Effects						
Children aged 6 months to <36 months across the 6 vaccine groups						
L AEs	tenderness	%	11.8 to 22.9	N/A		
	erythema		5.7 to ~8			
S AEs	diarrhoea	%	11.1 to 28.6			

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	irritability		11.4 to 27.8			
	sleepiness		8.8 to 25.7			
	fever (⩾38.0° C)		2.8 to ~14%		Uncertainty: in younger children fever ≥38 °C slightly more frequently reported in Arm F compared to other arms, only after the first vaccination	
Children 3 years to <9 years across the 6 vaccine groups						
L AEs	pain	%	from 13.5% to 36.1%	N/A		
S AEs	fatigue	%	2.9 to 18.2			
	headache		5.4 to 11.1			
	Fever (⩾38.0° C)		2.8 to 10.8			

Abbreviations: SCR: seroconversion rate; L AEs: solicited local adverse events; S AEs: solicited systemic adverse events.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH conducted a dose-finding study in subjects aged 36 months-<9 years in order to investigate which among the 6 different antigen/adjuvant doses proposed could be more appropriate for paediatric population.

Overall, the results indicate that Aflunov is immunogenic in children from 6 months to <9 years of age with increased antibody titers at 3 weeks after the second dose for all treatment arms, confirming that the 2-dose vaccine schedule is necessary to elicit immune response. Moreover, it was noted that subjects belonging to the younger age group (6–<36 months) displayed a higher immune response than older subjects (36 months-<9 years), suggesting that not-primed immune system in children enhances vaccine response.

Across age cohorts all immunogenicity data at three weeks as well as at 6 months after second vaccine dose support that a 100% MF59 content is needed in the monovalent H5N1 pandemic preparedness vaccine to elicit an increased immunogenicity compared to that achieved with lower adjuvant content.

Regards to antigen dose, no clear effect on immunogenicity is observed. While in vaccine arms D, E, F with 100% MF59 content, HI immune responses did not show relevant differences by increasing antigen dose, results obtained by MN assay seem to show slightly lower immune responses for Arm D compared to Arms E and F.

With regard to the safety profile, solicited local and systemic reactions from day 1 through day 7 appear to be similar among different H5N1 HA antigen doses and increasing MF59 content.

The number of subjects with solicited AEs tended to decrease with vaccination 2 compared to vaccination 1 in each study arm. Moreover, solicited systemic AEs seem to occur more frequently in younger children (aged 6 months to < 36 months) compared to those in the 3 years to <9 years age cohort.

3.7.2. Balance of benefits and risks

Among vaccine formulations with 100% MF59, the adult and half-adult antigen dose showed similar antibody responses and safety profile: while for the smaller antigen formulation a trend in lower immune responses was reported. Overall, no relevant reasons are identified for not supporting the use of vaccine full antigen-adjuvant dose (7.5 µg+100% MF59) also for the paediatric population (i.e., children and adolescents from 6 months to 17 years of age) as for the adult, when used in the context of a pandemic setting. It should be noted that Focetria was authorised and used with the same antigen-adjuvant dose as Aflunov in adult and paediatric populations (Immunogenicity and safety data with Focetria in paediatric population are currently reported in the Aflunov SmPC) and that previous study V87_P6 also tested full antigen-adjuvant dose for children from 6 months to 17 years.

3.8. Conclusions

The overall benefit-risk of Aflunov is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment of individuals 6 months of age and older for AFLUNOV, based on final results from study V87_30. This is a Phase 2, Randomized, Observer-Blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Several Doses of Antigen and MF59 Adjuvant Content in a Monovalent H5N1 Pandemic Influenza Vaccine in Healthy Pediatric Subjects 6 Months to < 9 Years of Age. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 5.4 of the RMP has also been approved. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the product information including updating the SmPC in line with EMA guidance regarding sodium and potassium content.

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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0189/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.