EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2023
EMA/CHMP/230680/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Foclivia

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

Procedure No. EMEA/H/C/001208/II/0081

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
aH5N1 Pandemic Influenza Vaccine H5N1 (surface antigen, inactivated, adjuvanted)
CI confidence interval
CRF Case Report Form
CRO Contract Research Organization
CSR Clinical Study Report
DMC Data Monitoring Committee
EC Ethics Committee
eCRF electronic Case Report Form
EDC Electronic Data Capture
EMA European Medicines Agency
FAS Full Analysis Set
FDA Food and Drug Administration
GCP Good Clinical Practice
GMR geometric mean ratio
GMT geometric mean titer
HA hemagglutinin
HI hemagglutination inhibition
ICF Informed Consent Form
ICH International Council for Harmonisation
ID identification
IM intramuscular
INN International Nonproprietary Name
IRB Institutional Review Board
IRT Interactive Response Technology
LAR Legally Acceptable Representative
LLOQ lower limit of quantification
MedDRA Medical Dictionary for Regulatory Activities
MN microneutralization
NA neuraminidase
NOCD(s) new onset of chronic disease
PFS prefilled syringe
PI Principal Investigator
PIP paediatric investigational plan
PPS Per Protocol Set
QTL quality tolerance limit
SAE serious adverse event
SAP Statistical Analysis Plan
SD standard deviation
SDA Source Document Agreement
SOP standard operating procedure
SRH single radial hemolysis
SUSAR suspected unexpected serious adverse reaction
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 28 November 2022 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, II and IIIB

Extension of indication to include children from 6 months to less than 18 years of age for Foclivia, 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 less than 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 4.9 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to bring it in line with the latest QRD template.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0085/2016 and P/0260/2018 on the agreement of a paediatric investigation plan (PIP) EMEA-001830-PIP01-15-M02. Moreover, the PIP was modified (P/0188/2020). A positive compliance check (EMEA-C-001830-PIP01-15-M02) was issued by the PDCO, considering that the measures are in compliance with the agreed above mentioned paediatric investigation plan and that the agreed timelines have been respected accordingly.

Information relating to orphan market exclusivity

Not applicable

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: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	28 November 2022
Start of procedure:	31 December 2022
CHMP Rapporteur Assessment Report	25 February 2023
PRAC Rapporteur Assessment Report	2 March 2023
PRAC Outcome	16 March 2023
CHMP members comments	21 March 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 March 2023
Request for supplementary information (RSI)	30 March 2023
PRAC Rapporteur Assessment Report	2 May 2023
PRAC members comments	3 May 2023
Updated PRAC Rapporteur Assessment Report	5 May 2023
CHMP Rapporteur Assessment Report	10 May 2023
PRAC Outcome	12 May 2023
CHMP members comments	15 May 2023
CHMP Updated Assessment Report	17 May 2023
2nd request for supplementary information (RSI)	25 May 2023
PRAC Rapporteur Assessment Report	26 June 2023
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	28 June 2023
PRAC Outcome	06 July 2023
CHMP Rapporteur's Assessment Report	07 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur's Assessment Report	17 July 2023
CHMP opinion:	20 July 2023

2. Scientific discussion

2.1. Introduction

Foclivia is a 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/0.5 ml dose.

Foclivia was granted approval under "exceptional circumstances" pursuant to Article 14(8) of Regulation (EC) n. 726/2004 on 23 July 2009 (EC decision issued on 18/10/2009), with the following "Conditions or restrictions regarding supply and use":

- Medicinal product subject to medical prescription
- Foclivia can only be marketed when there is an official WHO/EU declaration of an influenza pandemic, on the condition that the Marketing Authorisation Holder for Foclivia takes due account of the officially declared pandemic strain.
- In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose

and with the following "Specific obligations to complete post-authorisation measures for the marketing authorisation under exceptional circumstances", still applicable at the time of the present procedure:

Description	Due date
During the pandemic, the applicant will collect clinical safety and effectiveness data of the pandemic vaccine and submit this information to the CHMP for evaluation.	Depending on and after implementation of vaccine when first pandemic will take place.
During the pandemic, the applicant will conduct a prospective cohort study as identified in the Pharmacovigilance plan	Depending on and after implementation of vaccine when first pandemic will take place.

Foclivia is indicated for prophylaxis of influenza in an officially declared pandemic situation.

The initial marketing authorization application for Foclivia was handled as an informed consent of the Focetria EU application and, therefore, the data package in support of the initial Foclivia application was identical to that of the Focetria dossier.

Focetria is an influenza vaccine H1N1v (surface antigen, inactivated, adjuvanted) containing A/California/07/2009 (H1N1)-derived strain used NYMC X-181, 7.5 micrograms/0.5 ml dose. It was approved on 2 May 2007 as A/Vietnam/1194/2004 (H5N1). Following pandemic declaration in September 2009 the company submitted a type II variation (Pandemic Update (PU)/05) to change the strain from A/Vietnam/1194/2004 (H5N1) to A/California/7/2009 (H1N1)v like strain (X-179A). The MA of Focetria expired on 13 August 2015 following the decision of the MAH, not to apply for the renewal.

The H5N1 vaccine studies included in the original Foclivia dossier were conducted with monovalent MF59C.1 (MF59)-adjuvanted A/H5N1 influenza vaccine including either A/Vietnam/1194/2004(-like) antigen or A/H5N1/turkey/Turkey/1/2005(-like) antigen.

Since future pandemics might not be caused by a H5N1 virus, but might be due to another subtype of influenza virus (e.g. with haemagglutinin of type H1, H2, H7 or H9), Foclivia can only be marketed when there is an official WHO/EU declaration of an influenza pandemic and, in that case, the current strain will be replaced by the officially identified pandemic strain via a type II variation, in line with the regulatory pathway laid down in the Guideline on Influenza vaccines – Quality module (EMA/CHMP/BWP/310834/2012 Rev.1).

Seqirus is submitting a Type II variation for Foclivia to request an extension of indication based on the final results of Study V87_30 conducted to fulfil the post-authorisation commitments.

This dose-ranging study evaluated 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

Foclivia is a pandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted) indicated for prophylaxis of influenza in the case of an officially declared pandemic.

Foclivia's authorised posology in adults (from 18 to 60 years old) and elderly (over 60 years) is a single 0.5 mL dose containing 7.5 micrograms of H5N1 antigen and MF59C.1 adjuvant, containing 9.75 mg squalene, for intramuscular administration followed by a second dose after 3 weeks.

In children/adolescents under 18 years of age the safety and efficacy of Foclivia have not yet been fully established. Available data in children aged 6 months and 18 years of age are described in Section 5.1 of the SmPC.

Based on the data provided in the present application the MAH concludes "Selection of the optimal pandemic vaccine formulation for children requires consideration of several independent parameters, of which the benefit-risk profile, and the quality and longevity of the immune response are important factors. In addition, other factors such as logistics, vaccine production, distribution and use must also be considered. The immunogenicity and safety data support the selection of the 7.5 µg H5N1 antigen and 0.25 mL MF59 dose as recommend dose for the paediatric population. As this is the same dose currently licensed for use in adults, selection of this dose has the potential to minimize vaccination errors and to facilitate deployment in a pandemic setting. However, if alternative strategies in case of a pandemic are warranted (e.g. in the event of resource constraints with regards to antigen content due to challenges in the ability to manufacture sufficiently large amounts of vaccine), half the licensed adult dose (containing 3.75 µg H5N1 antigen and 0.125 mL MF59) or even formulations with a lower antigen dose including 0.25 mL MF59 could be considered in subjects 6 months to less than 9 years of age."

It should be noted that the currently approved Foclivia multidose vial presentation would allow withdrawing of different volumes to adjust different dosages.

Disease or condition

Influenza viruses are enveloped negative-strand RNA viruses (Orthomyxoviridae) containing a segmented RNA genome consisting of seven to eight gene segments, each coding for at least one protein.

At irregular intervals, the influenza viruses might undergo reassortment, the process of combining and rearranging virus gene segments that can occur when two differing influenza viruses, for example an animal and human subtype, co-infect a cell. Such reassortment process results in an antigenic shift that causes major changes in the influenza type A haemagglutinin (HA) antigen that, in turn, can result in the emerging of an influenza A virus capable of an efficient human to human transmission.

The emerging pandemic virus should be novel enough to prevail over the seasonal A viruses, and because of its novelty, there can be little specific immunity among humans, except for older people who may have met a similar virus in the past. This new influenza A virus can then spread rapidly from human to human all over the world causing a global outbreak of influenza disease that, because of the lack of human immunity, might cause a variable amount of severe disease and deaths.

Pandemics are different from seasonal outbreaks of influenza, as the latter are caused by subtypes of influenza viruses that are already circulating in the world whereas pandemics are caused by new subtypes or by subtypes that have not circulated among people for a long time.

Influenza pandemics are unpredictable and occur infrequently but have consequences on human health and economic well-being (WHO, 2017). Previous experience with the 2009 swine-origin influenza A(H1N1) pandemic showed that children were the most affected age category (Jain, 2009; Miller, 2010), probably due to higher exposure in schools or the lack of pre-existing immunity as seen in the elderly, who have likely encountered the virus earlier in life (Cobey, 2017).

State the claimed the therapeutic indication

In the present application the MAH proposed the following extension of the authorised indication:

"Prophylaxis of influenza in an officially declared pandemic situation in persons 6 months of age and older.

Foclivia should be used in accordance with Official Guidance".

The request for the extension of the age indication for Foclivia is based on safety and immunogenicity results of Study V87_30, 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.

Epidemiology and risk factors, screening tools/prevention

Influenza usually occurs in winter outbreaks or epidemics (in temperate climates). People of all ages are afflicted, but the prevalence is greatest in school-age children; disease severity is greatest in infants, the aged, and those with underlying illnesses.

An influenza pandemic occurs when a new influenza virus appears against which the human population has no immunity, and the emergent virus acquires the capacity to spread efficiently in humans. This can result in simultaneous epidemic disease in many locations worldwide, with substantial number of deaths and illnesses. Preceding the 2009 H1N1 pandemic, the last century witnessed three influenza pandemics, the "Spanish Flu" in 1918–1919, the "Asian Flu" in 1957 and the "Hong Kong Flu" in 1968 [Kilbourne, 2006], all arising from avian influenza viruses.

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.

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, B, and C, the first two are associated with significant seasonal morbidity and mortality.

Type A viruses, which are able to cause pandemics, are further subdivided according to their envelope glycoproteins with haemagglutinin (HA) or neuraminidase (NA) activity.

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 and stage/prognosis

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.

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 an influenza pandemic, vaccines are the most effective means of preventing and controlling the spread of influenza in the human population.

Foclivia is a monovalent pandemic influenza vaccine, surface antigen, inactivated, egg-derived, adjuvanted with MF59, manufactured with the same process and has the same adjuvant used for a centralised authorised seasonal influenza vaccine "Fluad Tetra" (Seqirus, 65 years of age and older).) and a nationally authorised seasonal Influenza vaccine "Fluad" (Seqirus, 65 years of age and older), a trivalent influenza vaccine licensed in several EU countries through a Mutual Recognition Procedure (MRP).

In order to provide a suitable network capacity for Foclivia in support of pandemic preparedness, different manufacturing sites are currently approved. With reference to Drug Product manufacturing activities, several manufacturing sites resulted currently approved for the manufacturing of either the pre-filled syringe (PFS) Foclivia presentation (3 manufacturing sites) or the multidose vial presentations (2 manufacturing sites).

2.1.2. About the product

Foclivia is an egg-based monovalent pandemic influenza vaccine (surface antigen, inactivated, MF59C.1 adjuvanted).

The vaccine contains purified HA and NA surface antigens from an influenza virus with a pandemic potential. In the event of an influenza pandemic being declared, the Foclivia Drug Product would be modified accordingly with the declared strain.

The MF59C.1 adjuvant is an oil-in-water emulsion, composed mainly of squalene that is an intermediate metabolite in the synthesis of cholesterol.

The vaccine is presented as a suspension for injection. The following presentations are actually authorised in EU for Foclivia:

Strength	Pharmaceutical Form	Route of administration	Immediate Packaging	Content (concentration)	Pack size
15 µg/ml	Suspension for injection	Intramuscular use	pre-filled syringe (glass) with needle	0.5 ml	1 pre-filled syringe
15 µg/ml	Suspension for injection	Intramuscular use	pre-filled syringe (glass) with needle	0.5 ml	10 pre-filled syringes
15 µg/ml	Suspension for injection	Intramuscular use	vial (glass)	0.5 ml (1 dose = 0.5 ml)	10 vials (monodose)
15 µg/ml	Suspension for injection	Intramuscular use	vial (glass)	5.0 ml (1 dose = 0.5 ml)	10 vials (multidose: 10 doses)
15 µg/ml	Suspension for injection	Intramuscular use	pre-filled syringe (glass) without needle	0.5 ml	1 pre-filled syringe
15 µg/ml	Suspension for injection	Intramuscular use	pre-filled syringe (glass) without needle	0.5 ml	10 pre-filled syringes

Since Foclivia can only be marketed when there is an official WHO/EU declaration of an influenza pandemic, no Foclivia batches have ever been manufactured and released in the EU market since the date of marketing authorization granting.

Foclivia is indicated for the prophylaxis of influenza in an officially declared pandemic situation and should be used in accordance with Official Guidance. The product is not indicated for prophylactic use during the pre-pandemic period.

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

Development programme

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 paediatric investigational plan (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)*

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

2.1.4. General comments on compliance with GLP, GCP

The clinical trial V87_30 included in this application was conducted partly outside the European Union (Philippines). The MAH stated that all trials were conducted in accordance with Good Clinical Practice (GCP) according to 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 were 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 provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol number	Title of the study	Date of inspection	Site (Full address)	Regulatory Agency
V87_30	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	27-28 Jan 2021	**Site 23301:** Clinical Research Centre, Sõbra 54, Tartu 50106, Tartumaa, Estonia.	State Agency of Medicines, Nooruse 1, Tartu EE-50411, Estonia.
		N/A NO GCP inspections have taken place	**Site 23302:** Al Mare Perearstikeskus OU, Paldiski mnt 68A, Tallinn 10617, Harjumaa, Estonia.	
		N/A NO GCP inspections have taken place	**Site 60801:** Philippine General Hospital, Room 2, Clinical Research Facility, Taft Avenue, Manila 1000, Philippines.	Food and Drug Administration (FDA), 1781 Civic Drive, Filinvest City, Alabang, Muntinlupa City, Philippines
		N/A NO GCP inspections have taken place	**Site 60802:** Philippine General Hospital, Taft Avenue, Manila 1000, Philippines.	
		N/A NO GCP inspections have taken place	**Site 60802:** Philippine General Hospital, Taft Avenue, Manila 1000, Philippines.	
		N/A NO GCP inspections have taken place	**Site 60804:** University of Perpetual Help, Dalta Medical Center, B006 Basement, De La Salle Health Sciences Institute, Dasmarinas, Cavite 4114, Philippines.	
		N/A NO GCP inspections have taken place	**Site 60805:** De La Salle Medical and Health Sciences Institute, Gov. D. Mangubat, Avenue (formerly Congressional Road), Dasmarinas, Cavite 4114, Philippines.	

2.4. Clinical efficacy

2.4.1. Main study

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

This 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 enrollment 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 enrollment and each participant was to be followed for a period of 12 months after receipt of the second dose of study vaccine.

Based on the final results from Study V87_30, that was included in the initially agreed EMEA-001830-PIP01-15, the MAH submitted a Type II variation for the extension of the age indication for Foclivia, a pandemic preparedness vaccine (formerly known as 'mock-up' vaccine)

For this vaccine, the strain will be updated with the pandemic strain before its use during the pandemic and hence paediatric use is relevant.

Consistent with the relevant GL on DOSSIER STRUCTURE AND CONTENT FOR PANDEMIC INFLUENZA VACCINE MARKETING AUTHORISATION APPLICATION (EMEA/CPMP/VEG/4717/2003) the MAH submitted the core pandemic dossier including immunogenicity and safety data obtained with the mock-up vaccine containing the influenza virus to which most or all of the population have no detectable immunity.

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 enrollment 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 enrollment 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 vaccines" 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 431

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 day
- 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 enrollment 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 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.

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.

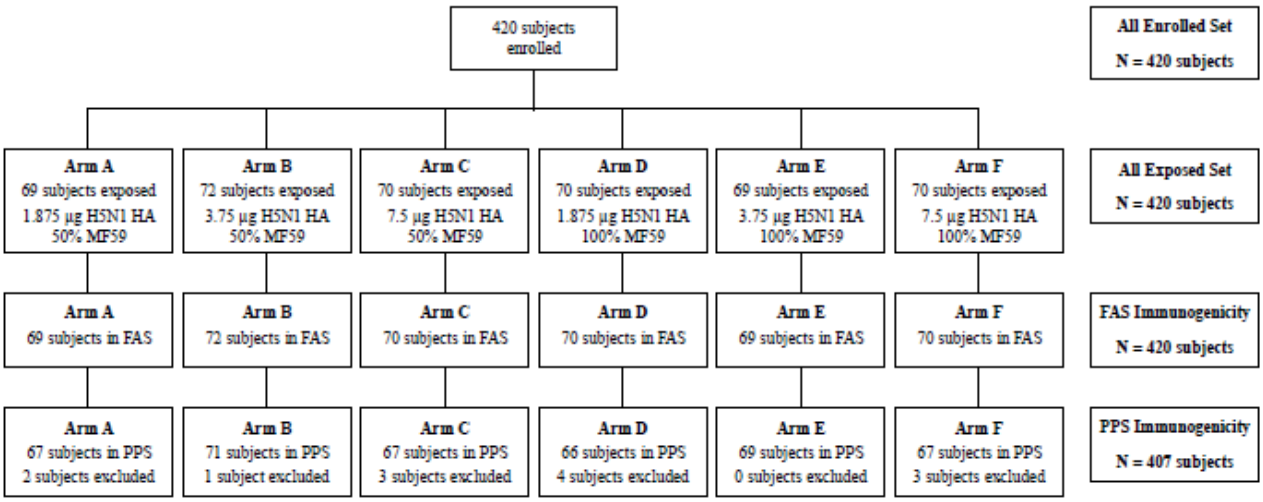
Results

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



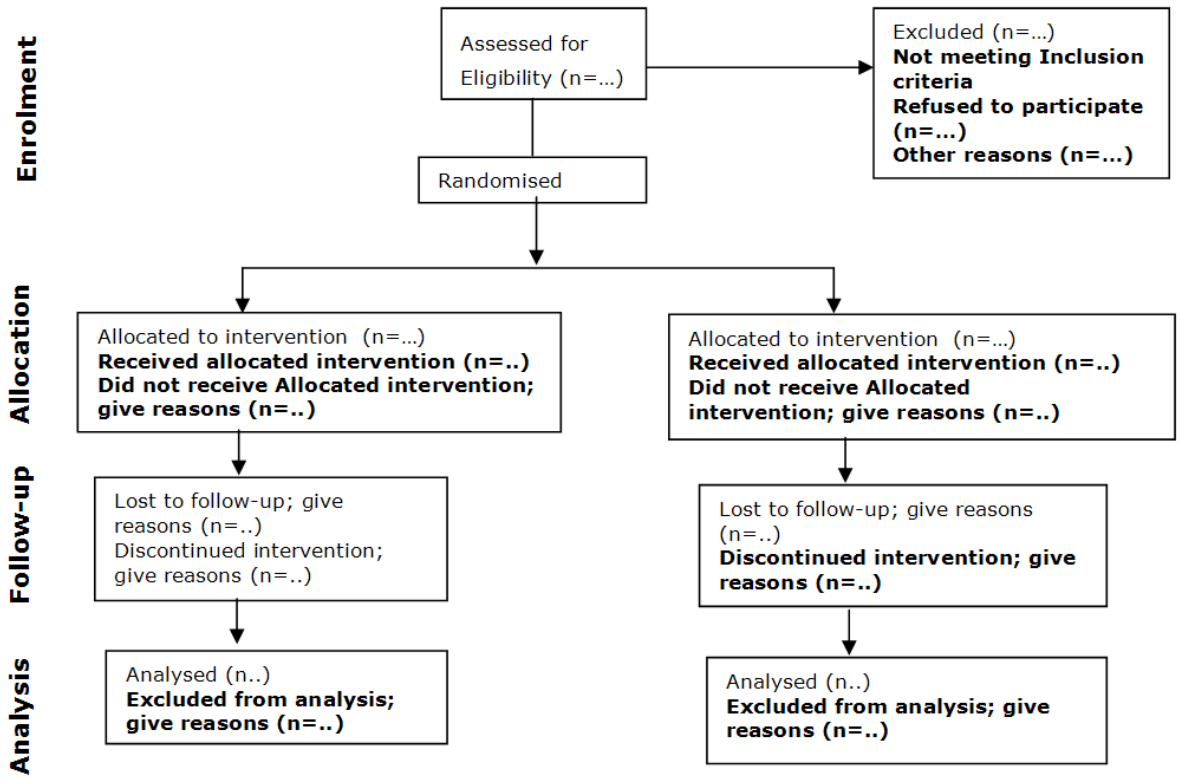
Source: Table 14.1.1.1 and Table 14.1.1.1.1.
Abbreviations: FAS = Full Analysis Set; HA = hemagglutinin; PPS = Per Protocol Set.

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 and in the Philippines.

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.

The study enrolled 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

The mean age of the study population was 49.3 months (SD: 30.82 months) consistent with the intended study population.

The age distribution shows a balanced stratification 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). 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.

Demographic and baseline characteristics are similar and balanced across vaccines subgroups with the exception of a slightly higher proportion of males (228/54.3%) as compared to females (45.7%).

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.

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 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.

Approximately 25% of subjects reported at least one medical disorder at medical history.

The use of prior and concomitant medications was balanced across the 6 vaccine groups; the most commonly reported types of prior and concomitant medications were viral vaccines (26.7%) and paracetamol (12.4%), respectively. Compliance was very high, with all of the 420 enrolled subjects receiving both the first and second study vaccination.

Numbers analysed

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

68.2%, 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

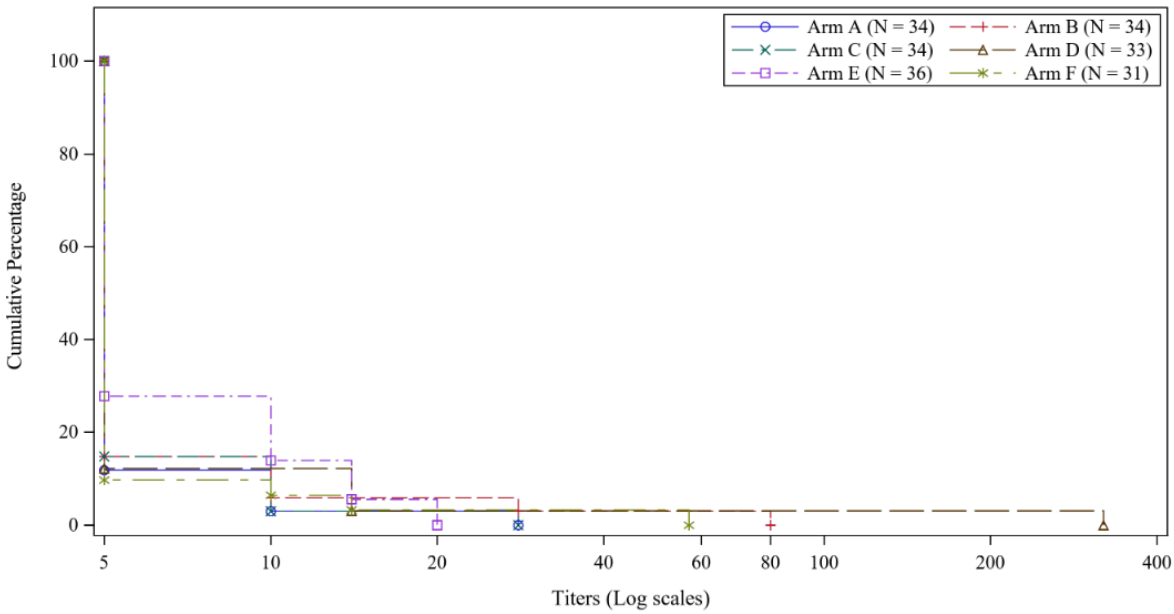


Figure 2: Reverse Cumulative Distribution Curves of HI Antibody Titers for the H5N1 Pandemic Influenza Homologous Strain by Vaccine Group on Day 22 in Subjects 6 Months to<36 Months – PPS Immunogenicity

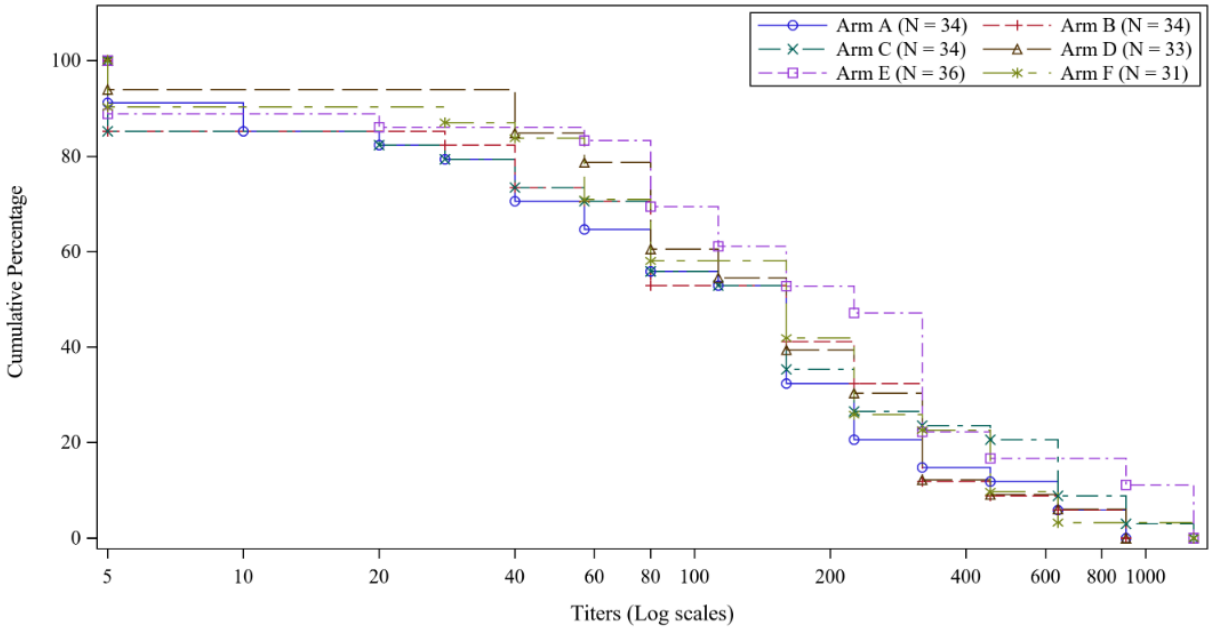


Figure 3: Reverse Cumulative Distribution Curves of HI Antibody Titers for the H5N1 Pandemic Influenza Homologous Strain by Vaccine Group on Day 43 in Subjects 6 Months to <36 Months – PPS Immunogenicity

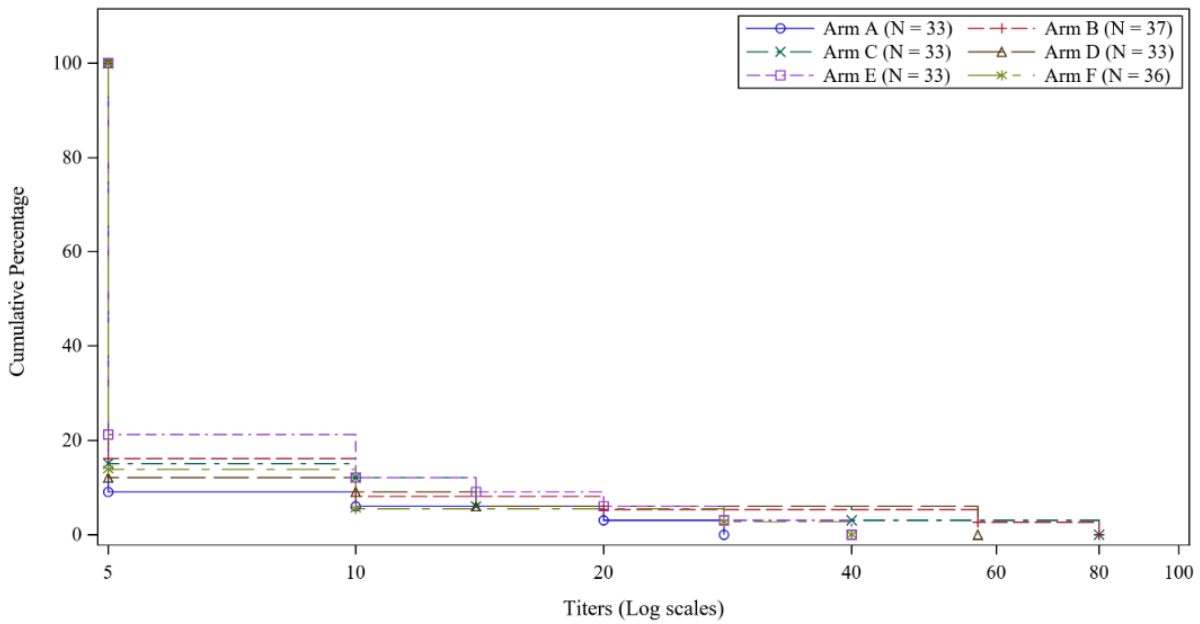


Figure 4: Reverse Cumulative Distribution Curves of HI Antibody Titers for the H5N1 Pandemic Influenza Homologous Strain by Vaccine Group on Day 22 in Subjects 3 Years to <9 Years – PPS Immunogenicity

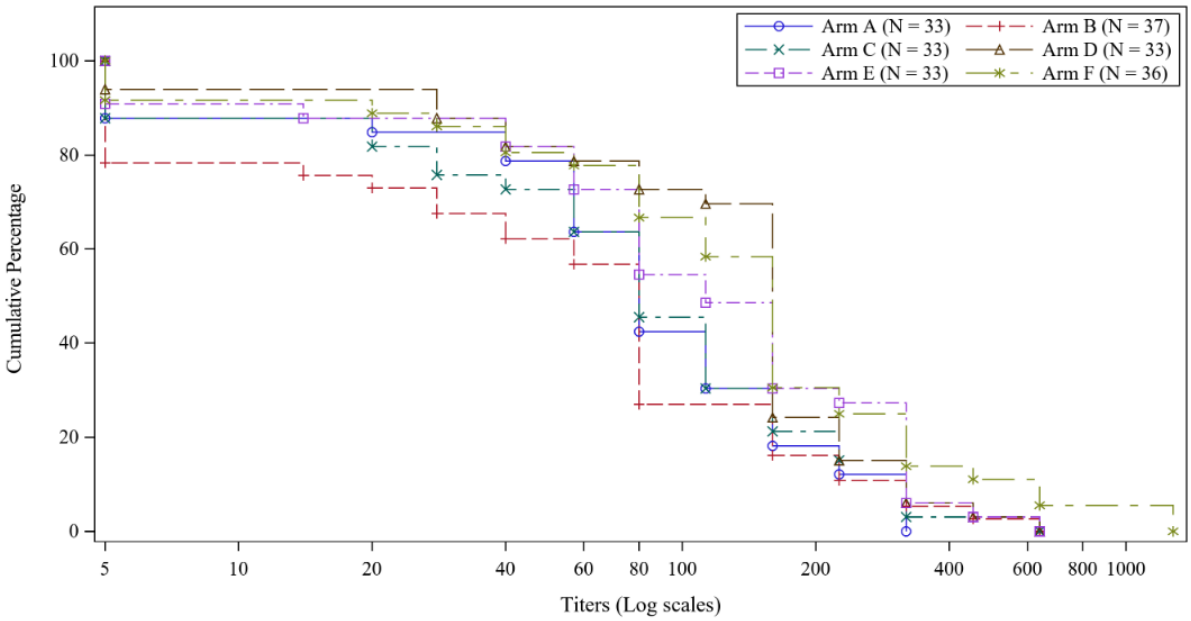


Figure 5: Reverse Cumulative Distribution Curves of HI Antibody Titers for the H5N1 Pandemic Influenza Homologous Strain by Vaccine Group on Day 43 in Subjects 3 Years to <9 Years – PPS Immunogenicity

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

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

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 E		3.75 µg HA/100% MF59, 12 months, n=69
	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)	**97.0** (89.48, 99.63)
Notes							

2.4.2. Discussion on clinical efficacy

Foclivia is a surface antigen, inactivated, egg-derived, adjuvanted MF59C.1 monovalent H5N1 pandemic preparedness vaccine (formerly known as 'mock-up' vaccine) containing A/Vietnam/1194/2004 strain (licenced formulation 7.5 micrograms/0.5 ml dose) intended for prophylaxis of influenza in an officially declared pandemic situation.

In a pandemic situation, children may be very vulnerable to infection and so constitute a special target group for vaccination. The PIP initially agreed by the Paediatric Committee (PDCO) EMEA-001830-PIP01-15 for clinical development of Foclivia in children and adolescents included the following two clinical studies:

- **V87P6**, a randomized, controlled, observer-blind, single-centre study to evaluate the immunogenicity, safety and tolerability of two doses of FLUAD H5N1 (Aflunov, surface antigen, inactivated, adjuvated) influenza vaccine in paediatric subjects from 6 months to less than 18 years of age (study V87P6, same as Study 1 of PIP EMEA-000599-PIP01-09-M04 and subsequent modification thereof). This study investigating only one dose of the vaccine (licenced formulation 7.5 micrograms/0.5 ml dose) and was completed at the time of the initial PDCO review (Variation II/07 adopted on 21/03/2012). Results are already included in section 5.1 of the SmPC.
- **V87_30**, a 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 from 6 months to less than 9 years of age (study V87_30, same as Study 3 of PIP EMEA-000599-PIP01-09-M04 and subsequent modification thereof). This study was conducted as a post-authorization commitment to provide additional clinical data on a paediatric aH5N1 dose.

Subsequently, based on the MAH's request on 10 December 2019 to apply changes to the timelines of Study V87_30 by delaying the start (from June 2020 to December 2020) and completion (from April 2022 to October 2022) of the study by 6 months, the PIP was modified with a positive opinion by the PDCO (P/0188/2020).

With this variation the MAH asked for amending the currently broad/general indication wording in: "Prophylaxis of influenza in an officially declared pandemic situation in persons 6 months of age and older" based on the results from study V87_30. However, as Foclivia in the pre-pandemic phase is authorised but cannot be marketed, definition of indication and up-dating of section 4.1 in the SmPC must be postponed in the event an H5N1 pandemic is declared, and a fast-track evaluation of a new vaccine that includes the virus strain causing the pandemic is carried out. Thus, the general indication should be maintained until the pandemic variation application, according to procedural requirement for influenza vaccines (EMA/56793/2014), is submitted. This is in accordance with previous analogous

procedures. Nevertheless, the posology section has been updated including individuals from 6 months of age for which the same adult dose/schedule (two doses (0.5 ml each), 21 days apart) is applied.

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 and conduct of clinical studies

Design

Study V87_30 is 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 enrollment 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 $\geq$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 Foclivia is immunogenic in children from 6 months to <9 years of age. However, the indication proposed by the MAH in 4.1 section of the SmPC (Prophylaxis of influenza in an officially declared pandemic situation in persons 6 months of age and older) cannot be agreed. As foreseen for pandemic preparedness vaccines (previously known as "mock-up" vaccines"), the general indication has been maintained to allow flexibility of use during a pandemic. This is in accordance with previous analogous procedures.

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 three 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.

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

The highest percentages of subjects with an antibody titre $\geq$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 adult and half adult antigen dose showed similar antibody responses, while for the smaller antigen formulation a trend towards lower immune responses were reported. Therefore, in principle the proposed dose for the paediatric population, that is the same as for adults (7.5 µg+100% MF59), sounds reasonable. This is also supported by results from study V87_P6 in children 6 months to 17 years of age and by Focetria that was approved and used with the same antigen-adjuvant adult dose as Foclivia both in adult and paediatric populations. However, according to SmPC guideline, section 5.1 also mentions immunogenic results from half adult antigen dose showing a comparable elicited antibody response vs full antigen dose.

2.5. Clinical safety

Introduction

The Safety profile of Foclivia in paediatric population comes from a dose-ranging paediatric study (V87_30) completed for aH5N1 in subjects 6 months through <9 years of age.

Study V87_30 was a 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.

A total of 420 subjects were enrolled in the study and randomized in a 1:1:1:1:1:1 ratio to one of 6 vaccine groups.

Solicited reactogenicity was recorded for 7 consecutive days (Day 1 through Day 7 and Day 22 through Day 28). Within this period, events were to be collected by the subject's parent(s)/LAR(s)/caregiver in a study specific daily Diary Card. All unsolicited AEs were collected during the treatment period (Day 1 through Day 43); and serious AEs (SAEs), new onset of chronic disease (NOCD), AEs leading to vaccine and/or study withdrawal, AEs of special interest (AESIs), and associated medications/vaccinations were collected during the follow-up period (Day 44 through Day 202).

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 Foclivia 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 Foclivia 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.

Solicited Systemic Adverse Events

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

(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 Foclivia SmPC referred to experience with H1N1v (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 Foclivia).

Serious adverse event/deaths/other significant events

SAEs

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 Foclivia, 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 Foclivia 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 Foclivia SmPC (section 4.8), regarding Focetria (H1N1) vaccine, while urticaria was moved from Focetria post-marketing section of Foclivia 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 Foclivia, 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 Foclivia in the paediatric population from Study V87_30 is similar to that known from StudyV97P6. 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 4.11 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.11.

The MAH submitted an updated RMP with proposed amendments mainly reflecting the results of the V87_30 clinical study and the safety data in the paediatric population. This paediatric dose-ranging study was designed to evaluate the safety and immunogenicity of six aH5N1 vaccine formulations (3 amounts of H5N1 HA antigen in combination with 2 dosages of MF59 adjuvant), administered as 2 vaccinations given 3 weeks apart in subjects 6 months through <9 years of age (420 subjects). The main proposed RMP changes were the following:

- Inclusion of V87_30 data in the clinical exposure sections
- Inclusion of indication and posology for children 6 months to less than 18 years of age in the product overview for Foclivia;
- Removal of missing information: *Use in children (6 months to less than 18 years of age)* from the list of the safety concerns.

Safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	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.

Safety Specification

Epidemiology of the indications and target population

Minor revisions to the PART II. MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) were proposed by the MAH and agreed.

Clinical trial exposure

The estimated subject exposure in completed clinical studies, the tested dose combinations and formulations have been updated in the text and the tables in order to include data from V87_30 study.

Populations not studied in clinical trials

The section has been updated by adjusting exposure data to the current available data and reviewing the limitations with respect to exposure in special populations. In particular the section related to the "Limitations in respect to populations typically under-represented in clinical trial development programmes" has been revised to bring up to date the knowledge on the vaccine use in children according to the results from V87_30 study. The MAH states that "there is no indication that the safety profile of aH5N1 influenza vaccine in the paediatric population (6 months to less than 18 years) differs from the adult and elderly populations characterised so far. No safety concerns have been identified form the paediatric population." Based on available data, the use in children of this vaccine is no longer considered a safety concern (missing information).

Post-authorisation experience

The section has been updated to current available data. Aflunov is largely sold to government parties for stockpile purposes and no doses were sold to the open market. No doses of Aflunov or Foclivia were administered to patients.

Identified and potential risks

No modification to the identified and potential risks has been proposed by the MAH with respect to the previous version 4.0 of the RMP, approved within the procedure EMEA/H/C/001208/WS2151/0068 on 05 May 2022.

Concerning the *Use in children (6 moths to less than 18 years of age),* previously classified as missing information was proposed to be removed by the MAH and agreed.

Missing information

Use in children (6 moths to less than 18 years of age) previously classified as missing information was proposed to be removed by the MAH.

Seqirus conducted a randomised, observer-blind, multicentre clinical trial to evaluate the immunogenicity and safety in healthy children 6 months to <9 years of age of six different vaccine formulations including either 1.875, 3.75, or 7.5 µg HA of H5N1 influenza strain combined with either 0.125 mL or 0.25 mL MF59, in two IM injections administered three weeks apart (V87_30). The study was a post-authorisation commitment in Europe, as agreed in the paediatric investigational plan (PIP) with EMA/Paediatric Committee (Aflunov: EMEA-000599- PIP01-09- M07, Foclivia: EMEA-001830-PIP01-15-M02). The purpose of this study was to provide additional clinical data on aH5N1 vaccine in children in anticipation of an avian influenza pandemic. In total 420 paediatric subjects were included in the study, 210 subjects each in the 6 months to <36 months age cohort and the 3 years to <9 years age cohort.

The rates of solicited local and systemic adverse events (AEs) within seven days following each vaccination were comparable across the six vaccine groups in both the 6 months to <36 months and 3 years to <9 years age cohorts. The vaccine formulations with higher MF59 content, including the formulation with the highest H5N1 HA antigen dose, were not associated with increased reactogenicity. Across age cohorts and vaccine formulations, the majority of solicited local and systemic AEs were mild or moderate in intensity, with few severe events reported. Most solicited local and systemic AEs had an onset close to vaccination and were of short duration. No subjects reported severe fever during the study.

The rates of unsolicited AEs reported in the 21 days following any vaccination were comparable between the six vaccine groups. The majority of unsolicited AEs were mild in intensity and not related to the study vaccine.

The incidence of serious AEs (SAEs) was low; no SAE was assessed as related to the study vaccine. One subject reported an AE (asthma) leading to new onset of chronic disease; no subjects reported AESIs or AEs leading to vaccine and/or study withdrawal.

During the study, 1 death was reported due to an AE. 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 the Sponsor as not related to the study vaccine.

In conclusion, the six aH5N1 vaccine formulations were well tolerated and had comparable and acceptable reactogenicity and safety profiles in the study population. No new significant safety information was generated from this study.

After completion of the V87_30 study combined with the results from the previously conducted paediatric study with aH5N1 (V87P6), MAH considered that the safety of aH5N1 vaccine in paediatric population (6 months to less than 18 years of age) has been characterised and is no longer considered missing information. No new important identified or potential risks or safety concerns were identified from the study.

The study V87_30 was conducted in order to address the missing area of information related to the use of aH5N1 influenza vaccine in children. Data from this study does not raise safety concerns in this special population and the safety profile was similar to that observed in adult and elderly people.

Since the RMP is a common document for Foclivia and Aflunov vaccines, the need to maintain such missing information in the list of safety concerns for Aflunov only has been evaluated. Considering that the authorised indication of Aflunov vaccine concerns the adult population and a PIP is in place for this vaccine, the missing information "Use in children (6 months to less than 18 years of age)" is not applicable according to GVP guidelines. Based on the above, the deletion of this missing information is applicable to the common list of safety concerns.

Therefore, the removal of "Use in children (6 months to less than 18 years of age)" from the list of safety concerns as missing information is acceptable.

Pharmacovigilance plan

The Pharmacovigilance plan has been updated according to the completion of the study V87_30. The study was included in the previous version of the RMP among the Additional pharmacovigilance activities not required by regulators. Therefore, reference to this study has been removed form text and table III.3.1.

The modification proposed to the pharmacovigilance plan is acknowledged.

The MAH was asked to introduce some amendments in the RMP to correctly reflect obligation in Annex II of the PI for Foclivia and to ensure adherence to RMP guidance.

The plan for additional pharmacovigilance activities was requested to be revised in accordance with Annex II conditions concerning the planned enhanced (active) safety surveillance consisting in a PASS imposed by the competent authority as a Specific Obligations in the context of marketing authorisation under exceptional circumstances. Therefore, this study should be categorised as cat 2 study. Timelines foresees that, in case of pandemic, a protocol designed with appropriate size and potency, with specific reference to the different age classes and special populations should be submitted for evaluation in line with EMA/CHMP/VWP/457259/2014 Guidance on Influenza Vaccines.

Furthermore, the V87_27OB study, a post-marketing observational cohort safety study of pandemic influenza A/H5N1** vaccine (Foclivia) in pregnant women should be reported as category 3 study since required to address the missing information "Use in pregnancy".

Information in Table Part III.3.1: On-going and planned additional pharmacovigilance activities should reflect the format and structure in line with Guidance EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2.

In the updated version of the RMP, the Table Part III.3.1 has been revised and agreed as follows:

Table Part III.3. 1: Ongoing 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 (Planned)	To evaluate safety and reactogenicity in terms of local and systemic adverse reactions in the different age groups	Not applicable	Protocol 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*

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.

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).

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

The structure and the content of the information reported are in line with Guidance EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2.

The MAH was requested to revise this Part of RMP in accordance with Annex II conditions.

In the updated version of the RMP, the Table Part IV.1 has been revised and agreed as follows:

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

Risk minimisation 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 and Aflunov 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 and Aflunov labels (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 and Aflunov SmPC; and Section 4 of the PL.
Vasculitis	Vasculitis is described in Section 4.8 Undesirable effects of the Foclivia and Aflunov SmPC; and Section 4 of the PL.
Guillain-Barré syndrome	Guillain-Barré syndrome is described in Section 4.8 Undesirable effects of the Foclivia and Aflunov 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
Use in pregnancy and lactation	Use in pregnancy and use during breast-feeding is described in Section 4.6 of Foclivia and Aflunov SmPC; and Section 2 of the PL.

The section has been modified by removing the reference to the missing information Use in children (6 months to less than 18 years of age) and the relative routine risk minimisation activities.

Furthermore, the routine risk minimisation activities have been updated for Immune thrombocytopenia. This safety concern has no activities planned since it has been included as a potential safety concern based on pharmacological class effects. No modifications to PI have been proposed with regard to this safety concern.

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

Annexes

The MAH submitted a revised version 4.11 of the RMP with annexes in line with GVP guidance**.**

2.7. Update of the Product information

No changes are made to the Opinion Annex II conditions. However, reference to the specific obligation set for in Annex II – E has been amended to introduce the obligation of conducting an Enhanced (Active) Safety Surveillance in turn of a prospective cohort study. This amendment follows the terms already agreed in the context of the EMEA/H/C/WS2151 procedure submitted by the MAH in order to revise RMP according to criteria in GVP Module V rev.2.

The proposal is considered acceptable since in line with EMA/CHMP/VWP/457259/2014 Guidance.

As a consequence of this variation, sections 4.2, 4.8 and 5.1 of the SmPC have been updated. Other minor changes have been included in the PI (see attachment). The Package Leaflet has been updated accordingly. Alignment with the current QRD template version v. 10.3 is ensured.

Section 4.2 of the SmPC

Posology
~~Adults and elderly (18 years of age and above): 0.5 ml at an elected date.~~
~~A second dose of vaccine should be given after an interval of at least 3 weeks.~~

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

~~Foclivia was evaluated in adults (aged 18 to 60 years old) and elderly (over 60 years old) following a 1, 22 day primary vaccination schedule.~~

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

Paediatric population

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

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

2.7.1. User consultation

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

As part of the present type II variation, the Foclivia SmPC has been updated to include the results of Study V87_30, provide more details on the other paediatric (Study V87P6), which was already described in the SmPC, and a few additional changes to further increase alignment within the document. The Foclivia PL has been updated in accordance with the changes in the SmPC and to increase alignment with the QRD template v.10.3.

The primary changes in the PL consist of the addition of more detailed nonserious 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. There are no changes to Contraindications, Warnings and precautions, Interactions, Pregnancy and breast-feeding or how the product is given (posology, dosage or method of administration).

Since none of the changes to the PL described above affect the safety profile, impact key safety information or how the product is used, conducting new consultation with target patient groups is not required.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Influenza is characterised by the occurrence of frequent, unpredictable epidemics, and much less frequent, worldwide pandemics. Influenza pandemic occurs when a novel influenza virus emerges against which the vast majority of the world’s population has no immunity. If such a virus demonstrates the ability to transmit efficiently from person to person, the result is a global outbreak of disease that affects a high percentage of individuals in a short period of time and is likely to cause substantially increased morbidity and mortality in all countries of the world.

Pandemics are different from seasonal outbreaks of influenza, as the latter are caused by subtypes of influenza viruses that are already circulating in the world whereas pandemics are caused by new subtypes or by subtypes that have not circulated among people for a long time.

Influenza pandemics are unpredictable and occur infrequently but have consequences on human health and economic well-being (WHO, 2017). Previous experience with the 2009 swine-origin influenza A(H1N1) pandemic showed that children were the most affected age category (Jain, 2009; Miller, 2010), probably due to higher exposure in schools or the lack of pre-existing immunity as seen in the elderly, who have likely encountered the virus earlier in life (Cobey, 2017).

Preceding the 2009 H1N1 pandemic, the last century witnessed three influenza pandemics, the "Spanish Flu" in 1918–1919, the "Asian Flu" in 1957 and the "Hong Kong Flu" in 1968 [Kilbourne, 2006], all arising from avian influenza viruses.

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 an influenza pandemic, vaccines are the most effective means of preventing and controlling the spread of influenza in the human population.

Foclivia is a monovalent pandemic influenza vaccine, surface antigen, inactivated, egg-derived, adjuvanted with MF59, manufactured with the same process and has the same adjuvant used for a centralised authorised seasonal influenza vaccine "Fluad Tetra" and a nationally authorised seasonal Influenza vaccine "Fluad", a trivalent influenza vaccine licensed in several EU countries through a Mutual Recognition Procedure (MRP). Four pandemic preparedness vaccines are currently authorised in the EU, which can be modified into pandemic influenza vaccines in a future pandemic.

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 enrollment 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 Foclivia 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 $\geq$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 Foclivia. 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. Regards to 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

Limited safety database

A total of 420 subjects aged 6 months to <9 years received Foclivia 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 Foclivia 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 26: Effects Table for Foclivia

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			
	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 Foclivia 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 authorized and used with the same antigen-adjuvant dose as Foclivia in adult and paediatric populations (Immunogenicity and safety data with Focetria in paediatric population are currently reported in the Foclivia SmPC) and that previous study V87_P6 also tested full antigen-adjuvant dose for children from 6 months to 17 years.

3.7.3. Additional considerations on the benefit-risk balance

Due to the pandemic nature of the vaccine, Foclivia MA remains under exceptional circumstances.

3.8. Conclusions

The overall B/R of Foclivia is positive. Posology for children aged 6 months 18 years has been added to

the Product Information.

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, II and IIIB

Extension of indication to include children from 6 months to less than 18 years of age for Foclivia, 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 less than 9 years of age. As a consequence, sections 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 4.11 of the RMP has been agreed. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to bring it in line with the latest QRD template.

Amendments to the marketing authorisation

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

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

Medicinal product subject to medical prescription

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

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

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Foclivia 001208-II-0081'.